DISEASES of the CHEST

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An Attempt to Produce a Unilateral Smoking Dog Using the Contralateral Lung as Control*

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The carcinogenicity of tobacco tar for the skin of mice was proved by Wynder, Graham, and Croninger in 1953.[1] Rockey and co-workers found that tobacco tar applied directly to the bronchial mucosa of dogs produced squamous metaplasia in 17 days. The same group stated that the ideal type of experimental exposure would be one that more closely simulated human exposure.[2] This, they state, would involve exposure of animals through some unique smoking device to tobacco smoke.

We have attempted to produce a unilateral smoking dog. The dog smokes cigarettes through a broncho-cutaneous fistula; the contralateral lung, not exposed to cigarette smoke, serves as a control.

The first method used was that of anastomosing a two inch piece of ⅜ crimped teflon to the distal end of the left bronchus. Using sterile operating room technique and sodium pentothal anesthesia, the left

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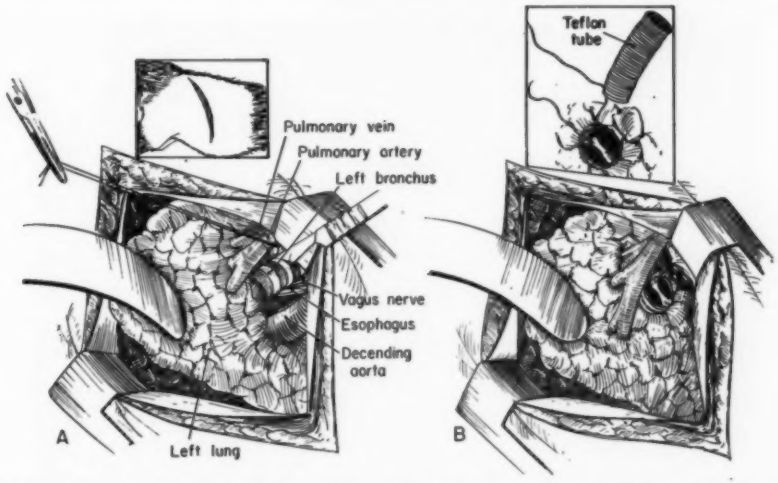

FIGURE 1A: Left mainstem bronchus as it is transected at carina. FIGURE 1B: Left main stem bronchus open at distal end plus tracheal end closed. Insert shows teflon tube being anastomosed to distal left bronchus.

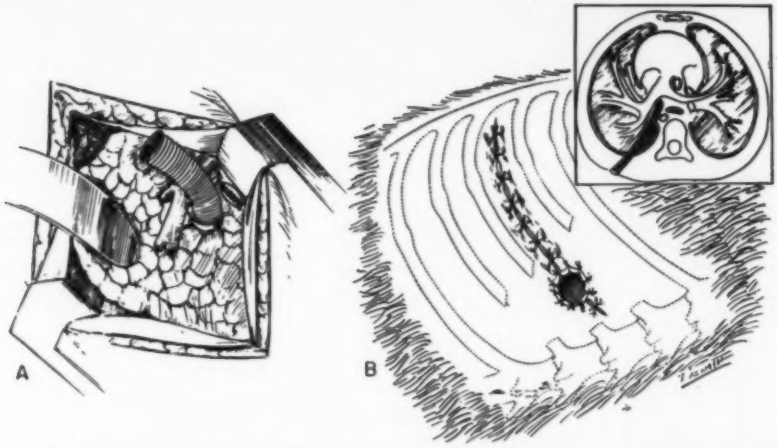

FIGURE 2A: Teflon crimped tube anastomosed to left main stem bronchus. FIGURE 2B: Completed operation with teflon tube stitched to left posterolateral chest wall. Note portion of 3, 4, and 5 rib removed. Insert shows venting method to ipsilateral chest wall.

thorax is opened through the fifth interspace. The pulmonary artery and vein are carefully dissected away from the left main stem bronchus which is, in turn, transected at its origin from the trachea (Figure 1A). The tracheal end of the bronchus is closed with interrupted 3-0 silk or catgut. The lung end of the bronchus was anastomosed to a short piece of crimped teflon (Figure 1B)—the same material used for arterial grafts. The teflon was brought through a button hole incision over the postero-lateral aspect of the chest (Figure 2A). Portions of the 4th, 5th, and 6th rib were removed to prevent obstruction (Figure 2B).

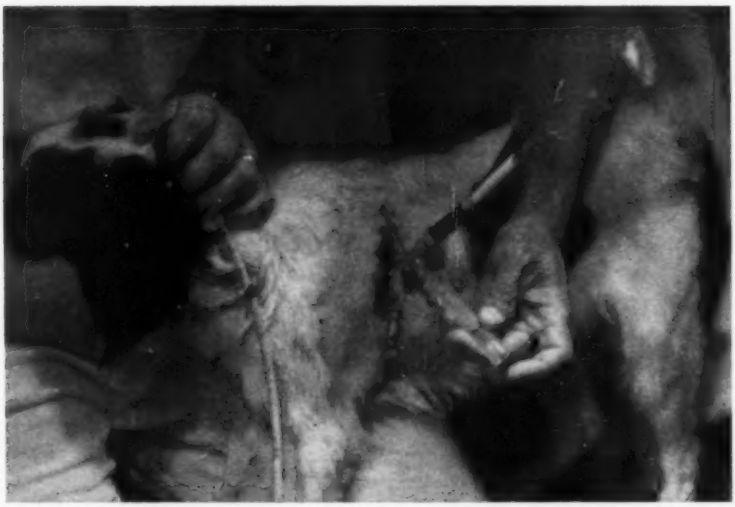

FIGURE 3: Smoking dog. The cigarette is consumed in about two minutes.

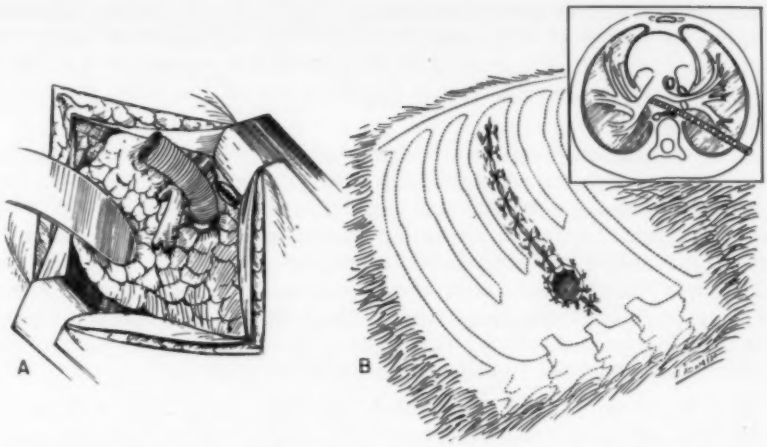

FIGURE 4B: Method of venting the left main stem bronchus through right postero-lateral chest wall. The length of ivalon is exaggerated for diagram purposes.

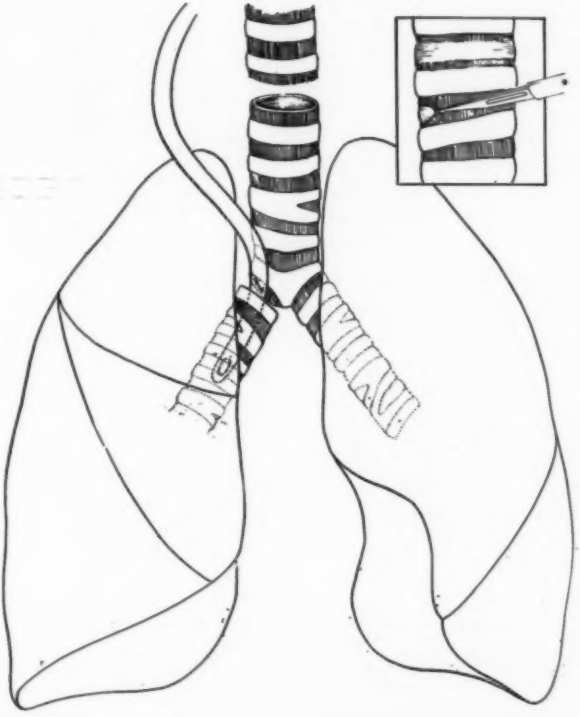

FIGURE 5: Tracheal graft in place with distal host trachea used to vent left bronchus to the rigth postero-lateral chest wall. Insert shows line of tracheal transection and method of supplying respiration while trachea is transected.

Immediately on recovery, these animals are able to smoke cigarettes (Figure 3). However, it is difficult to prvent angulation of the teflon bronchial junction; it is more difficult to maintain a clear air way. After 10 to 12 days the animals develop infection around the teflon graft and/or pneumonia.

Since angulation presented an obstruction problem, we attempted the same procedure from the right side of the chest. This time, the teflon conduit was brought through th right posterior chest wall (Figure 4B insert). Again the animal was able to smoke on recovery; but again the animal developed uncontrollable bronchial secretions, infection and pneumonia. Many minor alterations were made in technique—some of which included soaking the teflon in a solution of penicillin, preoperative antibiotics, and bathing the dog for three consecutive days before surgery. None of these has been effective in the long run.

Next we tried tracheal transplantation. This required sacrificing an animal to obtain a donor trachea which was substituted for the distal half of the host trachea. The distal host trachea plus the left main stem bronchus was brought out through the skin and musculature of the right chest wall. Again we used the right chest wall to vent the left lung so as to avoid angulation (Figure 5). Collapse of the tracheal graft,

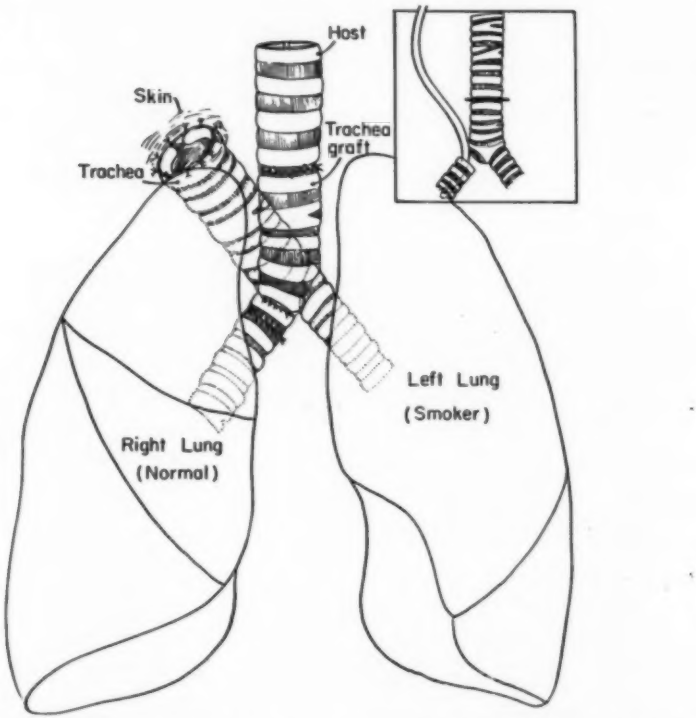

FIGURE 6: Method of ventilating dog while trachea is transected. Insert shows method of lengthening trachea by incising the annular ligaments between the tracheal rings.

pneumonia, and a newcomer (extensive, grotesque, subcutaneous emphysema) destroyed our smoking dogs in about 7 to 10 days.

The available animals are not the most healthy and vigorous. It seemed logical to produce, if possible, a unilateral smoker without use of any foreign material (homograft or otherwise). Klein reported that the trachea of the dogs may be stretched by successively incising to the depths of submucosa a sufficient number of the annular ligaments between the carilagenous rings.[3] Using this technique, it was possible to transect the right main stem bronchus at its origin, stretch out the trachea, transect six rings up from the carina, and directly anastomose the right main stem bronchus to the proximal trachea (Figure 6). The distal trachea with the left main stem bronchus is vented through the right postero-lateral chest wall. Again care is taken to avoid kinking or obstruction. The problem of relieving blood clots and secretions lead us

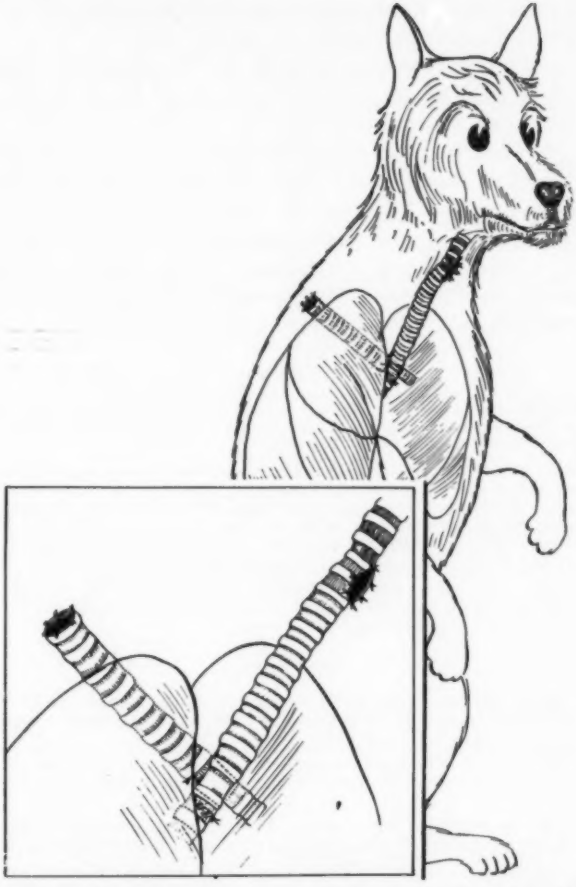

FIGURE 7: Proximal trachea anastomosed to the right main stem bronchus. The distal trachea vents the left main stem bronchus through the chest wall. Insert shows a close up of the operative procedure—note tracheostomy.

to the next step—that of concomitant tracheotomy (Figure 7). To a point, we can maintain a moderately clear tracheo-bronchial tree with ordinary suction. At post mortem examination, however, we find inspissated secretions far beyond our expectations.

The latest attempt is a more simple approach. The dog is operated through the right chest. A skin flap is prepared at the outset of the operation. The left main stem bronchus is divided at the carina and carefully anastomosed to the skin flap, so that the left main stem bronchus vents directly to the right postero-lateral chest wall. This technique resembles that shown in Figure 4B insert with the difference being the method of venting which in this case is a prepared skin flap.

Infection, pneumonia, and inspissated secretion still stumble us in our attempt to produce a long lived unilateral smoker. The longest survivor by any technique thus far is six weeks. This, of course, is totally inadequate. We suspect that preoperative antibiotics should be discontinued. It is mandatory that the newly operated animal should be kept in a heavily humidified environment.

Perhaps a tracheal prosthesis such as described by Moncrief and Salvatore of Walter Reed Army Hospital may be the solution.[4] They report experimental success with tygoflex, ap lastic prothesis for tracheal replacements. Perhaps with more assiduous tracheo-bronchial toileting and with a similar material, we may yet produce the smoking dog.

Dr. Oscar Auerbach has stated, ". . . over a ten year period I have not seen a case of bronchogenic carcinoma of squamous or oat cell (undifferentiated) who did not give a history of smoking."[5] It seems logical that we should put this thesis to the test with our autocontrolled unilateral smoking dogs.

SUMMARY

An attempt has been made to produce a dog which can smoke cigarettes through one bronchus. The contralateral lung is left in its normal position to serve as an auto control.

Several different techniques have been employed including a small piece of crimped teflon as conduit for the experimental bronchus, bringing the experimental bronchus to the contralateral chest wall, homologous tracheal grafts, and tracheal lengthening procedures. The most promising method to date has been that of preparing skin flaps from which a tube is fashioned and anastomosed to the left mainstem bronchus.

Regardless of technique, thus far, the animals have developed pneumonia, atelectases, empyema, tracheobronchial obstruction, or subcutaneous emphysema. A few dogs have lived as long as three or four weeks and have been able to smoke cigarettes readily through a one way valve system.

RESUMEN

Se intentó hacer que un perro pueda fumar cigarillos por uno de los bronquios. El pulmón contralateral es dejado en posición normal para que sirva como autocontrol.

Se han empleado varias técnicas, entre ellas una pequeña pieza de teflón estriado como un conducto hacia el bronquio en experiencia el que lleva a la pared torácica del lado opuesto, o bien por injertos traqueales homólogos o procedimientos de alargamiento del bronquio.

El método más prometedor hasta ahora, ha sido el de preparar colgajos cutáneos con los que hacen tubos que se anastomosan al tronco del bronquio principal.

Cualquiera que sea la técnica, hasta ahora, los animales han sufrido neumonía, atelectasia, empiema, obstrucción tranqueobronquial, o enfisema subcutáneo.

Unos cuantos perros han vivido hasta tres o cuatro semanas y han sido capaces de fumar cigarrillos facilmente a través de una válvula de un sentido.

RESUMÉ

L'auteur a tenté de préparer un chien de façon qu'il puisse fumer des cigarettes avec une seule bronche. Le poumon controlatéral est laissé dans sa position normale pour servir d'auto-contrôle.

Plusieurs techniques différentes ont été utilisées, comprenant un petit morceau de "teflon" servant de conduit à la bronche expérimentale, la mise de la bronche evpérimentale à la paroi thoracique controlatérale, des greffes trachéales homologues et des moyens d'allongement trachéal. La méthode qui a été la plus favorable jusqu'à ce jour consistait à préparer des lambeaux de peau à partir desquels un tube était façonné et anastomosé à la bronche souche gauche.

Indépendamment de la technique, autant qu'on puisse le penser, les animaux ont été atteints de pneumonie, d'atélectasie, d'épanchement, d'obstruction trachéobronchique, ou d'emphysème sous-cutané. Un petit nombre de chiens ont vécu pendant trois ou quatre semaines, et ont été capables de fumer des cigarettes à travers un système à valve unique.

ZUSAMMENFASSUNG

Es wurde ein Versuch unternommen, einen Hund so herzurichten, daß er Zigaretten durch einen Bronchus rauchen kann. Die kontralaterale Lunge wurde in ihrer normalen Lage belassen, damit sie als eine Selbstkontrolle dienen kann.

Verschiedene und differente Techniken wurden angewandt inschliesslich eines klienen Stückes eines gefalteten Teflon-Gewebes als Halt für den experimentellen Bronchus, um diesen mit der kontralateralen Brustwand zu verbinden, ferner homologe Luftröhrentransplantate und Verfahren zur Streckung der Trachea. Zur Zeit besteht die am meisten versprechende Methode darin, Hautläppchenherdstellen zu bilden, aus denen ein Tubus gebildet wird, der mit dem linken Hauptbronchus anastomosiert.

Unbeschadet der Technik trat bisher bei allen Tieren eine Lungenentzündung, Atelektase, Empyem, tracheobronchialer Verschluß oder subkutanes Emphysem aus. Einige wenige Hunde lebten immerhin drei oder vier Wochen und waren imstande, ohne besondere Umstände Zigaretten durch ein Einwegklappen-system zu rauchen.

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3 Klein, S. H., and Som, L.: "Extensive Segmental Resection of the Trachea with Primary Suture Anastomoses, An Experimental Study," Surgical Forum, American College of Surgeons, October, 1958.

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New Dimensions in Chest Radiography

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Traditionally in the United States, large size chest x-ray film examinations are made with 14 x 17 inch films in 15 x 18 inch cassettes. When a survey minifilm reveals a questionable disease process, large films are ordered for further study. This film has become the accepted size through years of routine practice. Its use is habitual and specified in practically all hospitals, clinics and doctors' offices throughout the country.

The fact that in practically all chest films there is often uselessly exposed film at the top and gray areas, representing the upper abdomen, at the bottom of each film has excited little, if any, comment. As in so many cases where the correctness of long established practices are viewed uncritically or taken for granted, no one has questioned the necessity for the 14 x 17 inch film size and little, if any, analysis has been made of effects in this vital area of the body exposed in such radiography.

A fresh look at this procedure by the radiologist has uncovered some revealing facts and figures—facts which make possible desirable reductions in x-ray film exposure, and figures which open the door to significant economy in film costs. If one looks at a 14 x 17 inch postero-anterior

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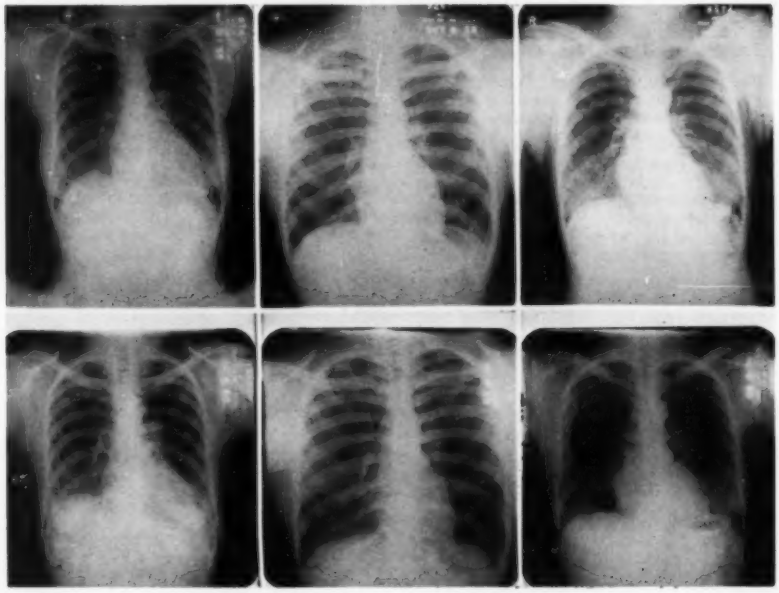

FIGURE 1: Chest radiographs of three types of patient showing exposure on 14 x17 film above and corresponding 14 x 14 inch film below. Waste of film and unnecessary exposure is demonstrated in the upper examinations.

film of the chest of an average man or woman, one sees wasted film above the shoulders and a gray void beneath the diaphragm. If three inches are eliminated at the bottom of the film, usually nothing of value is lost. Review of the postero-anterior chest films of 500 men and 500 women (including 200 pregnant women), in a total of five hospitals and clinics, revealed that a 14 x 14 inch film would be quite adequate for 98 per cent of the examinations (Fig. 1).

When it is considered that millions of 14 x 17 inch chest films are used in the United States yearly, the economy of reducing the exposed area by approximately 18 per cent is obvious. Probably in excess of 20 per cent of all x-ray film examinations are of the chest for surveys as well as for definitive diagnosis and follow-up examinations.

Rapidly increasing hospital costs make it imperative that such a saving be accomplished. Any measure which would promise reduction of spending of Federal funds as in the Armed Forces, Veterans Administration and the Public Health Service would be most welcome. In these government services alone, it is estimated that $1,500,000 per year could be saved in film costs.

Use of x-ray film has increased about 150 per cent in the past 10 years and it may be expected it will continue to rise. Money saved in making chest x-ray films could be used to buy many needed smaller sizes. At current prices, a box of standard 14 x 17 inch (75) films costs $56.65. A box of the same quality 14 x 14 inch (75) films costs $46.85. This represents a saving of $9.80 on each box and amounts to about $0.13 per film.

Even more important than the economy anticipated would be the reduction of radiation dose. A considerably smaller volume of tissue would be exposed to x rays. Because of the millions of examinations made each

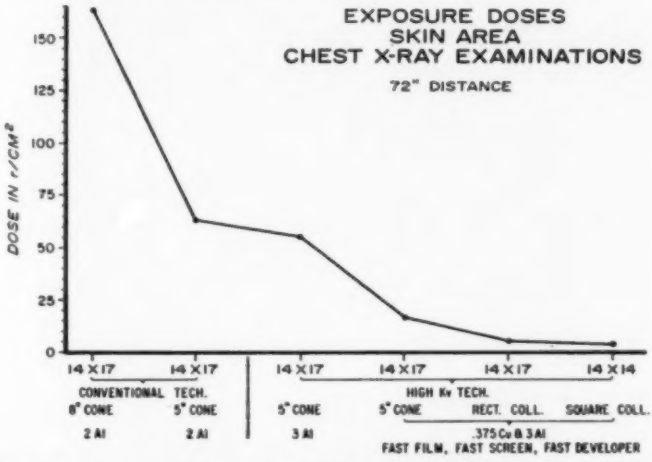

FIGURE 2: This bar indicates the total area exposed to ionizing radiation when conventional technique is used with an 8 inch cone or a 5 inch cone, 2mm. of aluminum filtration and a 14 x 17 inch film. Comparison of this technique with one using added filter, fast films, fast screns, fast developer, and additional copper as well as aluminum filtration with rectangular and square beam collimators indicates a tremendous reduction in skin area dose.

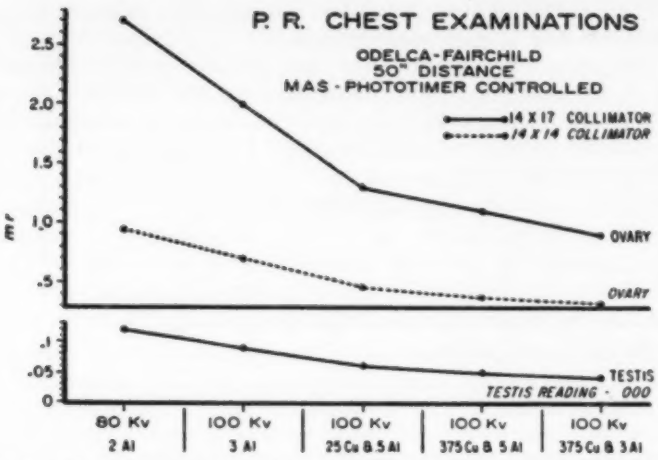

FIGURE 3: In this graph, using the Odelca Fairchild photoroentgen machine for chest x-ray film examinations, comparison is made of the doses to the gonads using a 14 x 17 beam collimation vs. a 14 x 14 collimation and increasing amounts of filter to achieve a negligible dose to the ovary and a vanishing dose to the testes.

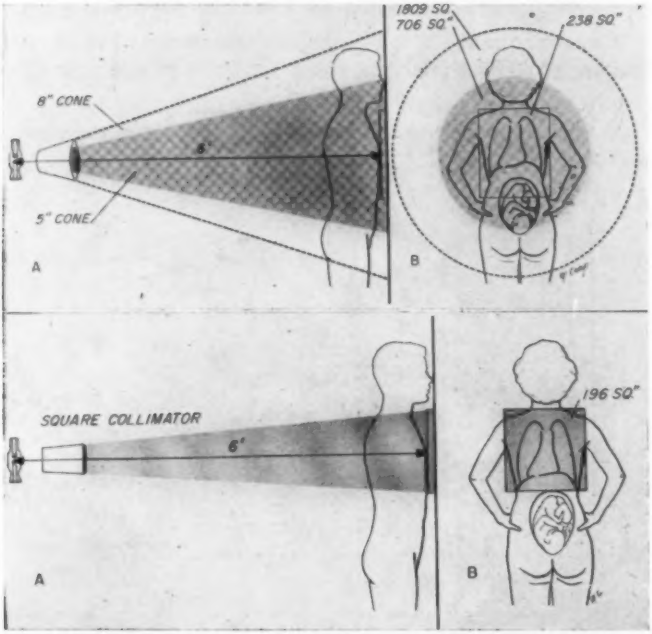

FIGURE 4: At "A" is shown a typical chest radiographic examination using either an 8" or 5" cone to cover a 15" x 18" cassette. Unnecessary exposure of the upper abdomen as well as other parts of the body are seen in "B".

FIGURE 5: "A" demonstrates positioning patient for 6 feet chest x-ray examination using a square beam collimator to exactly cover a 15" x 15" cassette shown at "B". The fundus of the uterus and gonads of the fetus are out of the direct beam.

year, this becomes important in relation to total population exposure to ionizing radiation. Conventional techniques for surveys using PR machines, in vogue in most states,[1] deliver doses to the skin in amounts of as much as 0.8r per PA film. With addition of 2 mm. of aluminum, this can be reduced about 60 per cent. By using higher kilovoltage, shorter time of exposure, fast films, hi-speed screens and aluminum combined with copper filters,[1] a tremendous reduction in dose can be achieved.[2] The use of a rectangular or square collimator* further reduces the volume dose and dose to the skin and gonads. Figures 2 and 3 show marked radiation reduction in the area exposed by using five inch instead of eight inch cones and marked further reduction of dose by using rectangular and square beam collimators with additional filters. The lowest

[1]Only Pennsylvania, New York, Michigan and Texas have laws requiring at least 2 mm. added filter in the x-ray tube.

*A special device adjustable with lights to outline square or rectangular fields used instead of cones which limit circular fields.

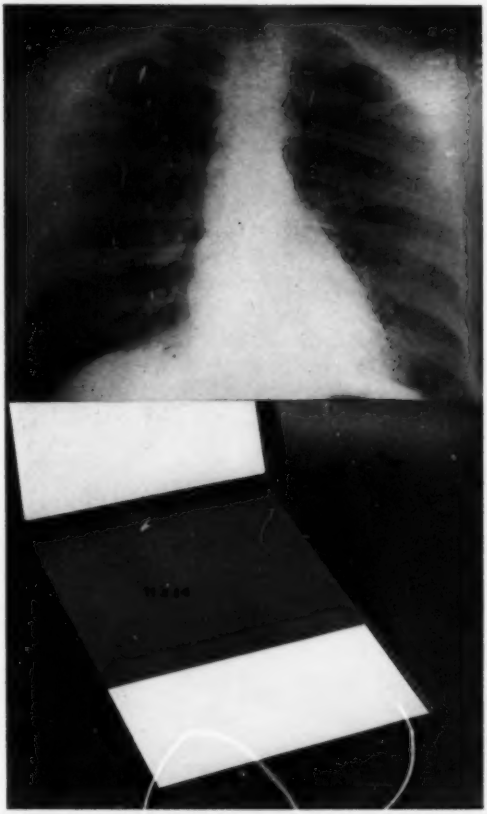

FIGURE 6: Radiograph of AP lordotic projection on an 11" x 14" film which clearly shows infraclavicular disease but not unnecessary exposure beneath the diaphragm.

FIGURE 7: Opened 15" x 18" cassette showing 11" x 14" film in place for AP lordotic projection of chest.

possible dose is obtained by combining all the factors viz, square beam collimation with 14 x 14 inch film size, fast films, fast screens, fast developer and copper with aluminum filters (Figs. 2 and 3).

X-ray technique is of particular importance in prenatal examinations. In the last trimester of pregnancy, the uterine fundus will almost always lie in the field of radiation when an exposure is made on a 14 x 17 inch area (Fig. 4). Inasmuch as the diaphragm is high during pregnancy, there is little difficulty experienced in getting all of the lung fields on a 14 x 14 inch film (Fig. 5). It is true that in many women, the chest can be completely visualized on an 11 x 14 inch film. Furthermore, since most presentations are cephalic, the gonads of the fetus are near the fundus and would be spared direct radiation when the square film with beam collimator is used. Geneticists are in general agreement that there is no threshold below which radiation may not be dangerous to the gonads. Certainly, inclusion of the developing embryo in utero would represent a most critical situation.[3,4,5]

Throughout the United States, many AP lordotic views of the chest are made to search for possible infraclavicular extension of disease (Fig. 6). In these views, the area of interest is positioned high on the film. At least the lower one-third, if not more, of the film is wasted, and is not needed for study. For this kind of view, it is suggested that an 11 x 14 inch film (commercially available) be used, placing it in the upper part of the 15 x 18 inch cassette (Fig. 7). As with the 14 x 14 inch film using

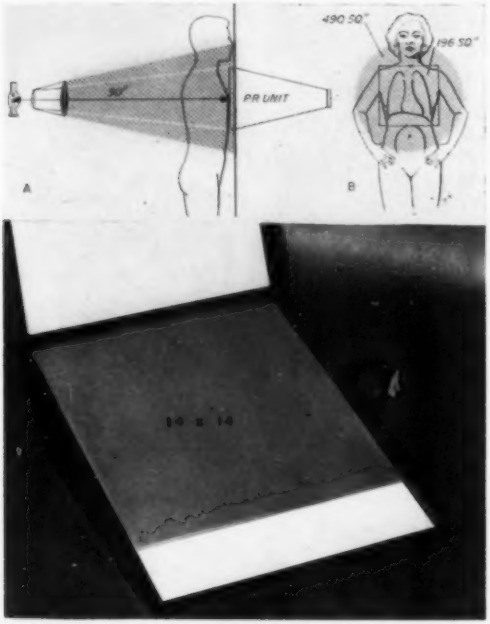

FIGURE 8: Use of a square beam collimator or cut-out lead aperture is illustrated in PR unit. Unnecessarily large field is irradiated with cone versus collimated beam adjusted to 14" x 14" area for production of 4" x 4" survey film.

FIGURE 9: Opened 15" x 18" cassette showing positioning of 14" x 14" film in upper portion where pressure of screens will retain it.

square collimation of the beam, a rectangular field of x rays would be projected to the area of interest, thus achieving a great reduction in dosage.

With the collimator adjusted for a square zone of radiation, the 14 x 14 inch film may be used equally well for lateral and oblique views of the chest. It will be necessary, and this may require close supervision and added training, for x-ray technicians to be more exact in positioning the patient and centering the beam to achieve uniformly good results.

A square beam collimator can also be used for minifilms when a 4 x 4 inch film can be substituted for one 4 x 5 inches (Fig. 8). There will result a small saving in cost but a considerable reduction in dosage because of irradiation of smaller volume of tissue.

There may be some questions about "retooling" for this procedure. The first thing to do is order 14 x 14 inch films and processing hangers for posterio-anterior, lateral and oblique chest x-ray film examinations. These are commercially available from suppliers. While it would be easier to buy and use 15 x 15 inch cassettes, this is not necessary. A 14 x 14 inch film may be placed in a 15 x 18 inch cassette by pushing it to the hinged end where the screen pressure will hold it in place (Fig. 9). When it becomes necessary to buy new cassettes to replace 15 x 18 inch ones, only 15 x 15 inch cassettes and screens need be purchased for chest x-ray film examinations, thus effecting another considerable saving in cost of equipment.

It is routine in many hospitals and clinics to make a film of the abdomen in addition to one of the chest. When 14 x 17 inch films are used for both of these examinations, there is obviously an overlap of radiation in the region of the diaphragm. Since anything less than a 14 x 17 inch film is not adequate for the adult abdomen, this double exposure can be prevented by use of a 14 x 14 inch chest film with square collimation.

SUMMARY

The advantages of a 14 x 14 inch film of the chest compared with a standard size 14 x17 inch one are as follows:

1) Saving of approximately 18 per cent in cost by purchase of the smaller size film. This figure is about $0.13 less per film and would represent a tremendous savings since millions of chest x-ray film examinations are being made in the United States today. A proportionately smaller total dollar saving but a higher percentage saving (20 per cent) would be effected by using a 4 x 4 inch film instead of the 4 x 5 inch one in photoroentgenography.

2) Lower volume doses to critical areas of the body as well as smaller skin and gonad doses are obtained when the beam collimator is used with a 14 x 14 inch film or the smaller 4 x 4 inch PR film.

3) Vital reduction of x-ray exposure to the mother and to the gonads of the fetus in prenatal x-ray examinations, either by using the 14 x 14 inch film or the 4 x 4 inch PR films.

RESUMEN

Las ventajas de la película de 14 x 14 pulgadas sobre la estandard de 14 por 17, son las siguientes:

1) Ahorro de aproximadamente el 18 por ciento de costo. Esto significa aproximadamente $0.13 menos por película, lo que es un tremendo ahorro ya que se hacen millones de películas de tórax en los Estados Unidos en la actualidad. Un ahorro proporcionalmente menor del total de dólares, pero un porcentaje mayor (20%) sería el obtenido usando películas de 4 x 4 pulgadas en lugar de 4 x 5 en roentgenografía.

2) Menor volumen de dosis de radiación sobre áreas más sensibles del cuerpo así como dosis menores sobre piel y gonadas se obtienen cuando se usa el colimador del haz con la película de 14 x 14 a con la de 4 x 4 en Roentgenfoto.

3) Reducción vital de exposición a los rayos X de las madres y de las gonados del feto con los exámenes prenatales, ya sea usando la 14 x 14 o la 4 x 4 en las respectivas técnicas.

RESUMÉ

Les avantages du film thoracique de 35 cm. x 35 cm. comparé à la dimension standard de 35 x 43 cm. sont les suivants:

1°) Une économie d'environ 18% du prix de revient par l'achat de film de taille plus petite. Ce chiffre est d'environ 0.13 dollar de moins par film et représenterait une économie énorme sur les millions d'examens radiographiques thoraciques qui sont actuellement pratiqués aux Etats-Unis. Une économie totale proportionnellement plus petite en dollar mais plus grande dn pourcentage (20%) serait effectuée en utilisant un film de 10 cm. x 10 cm. au lieu de 10 cm. x 13 cm. en radiophotographie.

2°) Des doses plus faioles en volume pour les zones critiques du corps ainsi que des doses cutanées et gonadiques plus petites sont obtenues quand on utilise un film de 35 x 35 cm. ou la radiophotographie plus petite de 10 10.

3°) La réduction vitale de l'exposition aux rayons pour la mere et pour les gonades du foetus dans les examens radiologiques prénataux, soit en utilisant le filb de 35 x 35 ou la radiophotographie de 10 x 10.

ZUSAMMENFASSUNG

Die Vorzüge eines 35.6 x 35.6 cm Filmes des Thorax im Vergleich zur Standardgröße von 35.6 x 43.2 cm sind folgende:

1.) Einsparung von etwa 18% der Kosten beim Einkauf des kleineren Formates. Dieser Wert liegt bei ungefähr 0.13 $ pro Film und würde eine ganz enorme Ersparnis bedeuten; werden doch heute in den USA Millionen von Thorax-Röntgenaufnahmen angefertigt. Eine verhältnismässig geringere Geldersparnis, jedoch eine höhere prozentuale Ersparnis (20%) würde erreicht bei Verwendung von 10 x 10 cm Filmen anstelle der 10 x 13 cm Filmen, die für die Schirmbildaufnahme gebraucht werden.

2.) Geringere Volumendosen für die kritischen Körperabschnitte ebenso wie nierigers Haut- und Gonaden-Dosen bekommt man bei Benutzung des Stahlen-Collimators in Verbindung mit einen Film der Größe 35.6 x 35.6 cm oder des kleineren 10 x 10 cm Schirmbildfilmes.

3.) Man erzeilt eine äusserst wesentliche Verringerung der Röntgenstrahlenbelastung für die Mutter und die Gonaden des Fötus bei vorgeburtlichen Röntgenuntersuchungen sowohl bei Verwendung des 35.6 x 35.6 cm Filmes wie auch des 10 x 10 cm Schirmbildfilmes.

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The Effects of Steroid Therapy on Pulmonary Tuberculosis*

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The exact status of steroid therapy in the treatment of pulmonary tuberculosis is far from clear. In the beginning, active and inactive tuberculosis were considered contraindications of adrenal steroid use.[7,14] In a second stage, treatment with them was admitted for non-tuberculous conditions in the presence of active tuberculosis always under antimicrobial coverage.[13] We reached, at last, the present phase, where the hypophyseal-adrenal hormones have a definite place in the treatment of certain forms or localisations of tuberculosis, leading to extremely encouraging results. Such are the instances of tuberculous meningitis, miliary, pleural, peritoneal and pericardial forms.[1,2,6,8,9] We will discuss further[4] the effects of hormonal therapy on pleural effusion.

The status of steroid therapy in tuberculosis is still subject to discussion and thorough investigation. Although its responsibility in the enhancement of a preexistent tuberculous process is well established,[5,14] it is also known that this detrimental effect may be overcome when used in conjunction with appropriate antimicrobial therapy.[2,13] Such concurrent therapy, as a matter of fact, seems to be a definite approach whenever pulmonary tuberculosis is on adrenal hormones treatment. It must be borne in mind, however, that such combination only will be successful when tubercle bacilli reveal susceptibility towards chemotherapeutic agents. We have been able to demonstrate[3] how tuberculostatic drugs fail to avoid the aggravating hormonal effect when tubercle bacilli show any degree of drug-resistance.

It has been an ultimate goal of therapeutics to use the favorable effects of hypophyseal-adrenal hormones in the treatment of pulmonary tuberculosis. The anti-stress effect, anti-allergic activity and the detoxifying effect in highly evolutive forms, besides their anti-phlogistic capacity and possible potentiation of antimicrobial drugs are some of the major advantages of these hormonal agents which make them so useful in the treatment of pulmonary tuberculosis.

In the present stage of experimental survey, it seems important to report our results in a series of 24 patients of the Institute of Phthisiology and Pneumology of the University of Brazil (Director — Prof. A. Ibiapina). The series include 13 cases reported in a previous paper.[3] A greater number of cases was subjected to treatment, but some were excluded from this study as they did not fulfill the conditions required.

Material and Methods

The clinical material consists of 24 women hospitalized in the ward Affonso Penna, Jr. (Institute of Phthisiology and Pneumology of the U. B.). These are cases of active pulmonary tuberculosis confirmed by

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clinical, roentgenographic and bacteriological trials (five were found to have sputum negative for acid-fast bacilli at the term of combined therapy with prednisone, although the sputum had been positive prior to treatment).

a — Extent of disease:
- Moderately advanced 4
- Far advanced 20

b — Bacteriological findings:
- Sputum positive 19
- Sputum negative 5

c — Tests for susceptibility to antimicrobial agents:
- Resistant (+) 7
- Susceptible 12
- Negative 5

(+) — Resistance level was assessed: 0.2 to INH, 2 to SM and 0.5 to PAS.

d — Clinical and miscellaneous tests:
- Roentgenographic tests and tomography, monthly.
- Sputum studies with culture and drug resistance tests, monthly.
- Determination of glycemia and potassium and sodium levels, monthly.
- Urine analysis, monthly.
- Pulse, temperature, blood pressure and weight daily.
- Routine diet.

e — All patients continued on associated treatment to which they were eventually submitted prior to present therapeutic procedures.

f — Therapeutic schedule was as follows: Prednisone 15 mg. daily during the first month, 10 mg. during the second and 5 mg. during the third month.

Antimicrobial coverage was performed with streptomycin at dosage of 1 g. daily and isoniazid, 10 mg. per kg. of body weight. (+)

g — *Indications for treatment were the following:*

1 — *Drug intolerance with hypersensitivity reactions:* 4 cases

In all these cases, the administration of the drugs usually prescribed (INH, SM or PAS) caused severe eczematoid rash or urticaria which subsided when drugs were discontinued and recurred with a new course. This fact, no doubt, represents a significant impediment to adequate therapeutic measures.

2 — *Inefficacy of long-term therapy with the purpose of potentiation:* 9 cases

These are representative cases of far advanced tuberculosis on long-term therapy that should be labelled as failures as they still displayed active disease needing treatment.

3 — *Acute pulmonary disease:* 8 cases

This group consist of the most important instances including five cases of miliary tuberculosis (one with coexisting meningitis) one case of caseous bronchopneumonia and two acute episodes, highly evolutive, in patients with pre-existing chronic pulmonary tuberculosis.

4 — *Associated conditions:* 3 cases

(+) The drugs employed in the present studies were: Meticorten, Streptomix and Ditubin kindly supplied by Schering Indústria Quimica e Farmacêutica S/A.

Two patients with pulmonary tuberculosis had associated asthma and in one, there was pleural effusion coexisting with the tuberculous disease.

With the above indications, an attempt was made to meet the following requirements:

a — In the cases of intolerance: anti-allergic effects.
b — In the cases of inefficacy: possible potentiating effect of prednisone on chemotherapeutic agents.
c — In the cases of acute disease: anti-inflammatory effects.
d — In cases of an associated disease: make use of prednisone when indicated in the treatment of coexisting conditions.

Results

Result will be evaluated by their clinical and roentgenographic aspects. Bacteriologic findings will not be assessed as the period of analysis was much too short to warrant any definite conclusion. The effects upon symptoms and roentgenologic changes are components capable of more accurate appraisal.

Results will be recorded only as:

a — Unchanged
b — Improved: whenever present symtomatic and roentgenographic improvement as a result of resorption of infiltrates and of improvement or closure of cavities.
c — Deterioration

Among the 24 cases placed on combined antimicrobial-steroid therapy eight became worse, 13 improved and three remained in the status prior to medication, as summarized below:

	No.	Per cent
Improved	8	33.3
Worse	13	54.1
Unchanged	3	12.5
Total	24	99.9

We shall discuss separately the distribution of these results in terms of bacterial susceptibility and clinical indications.

I — *Worse* (8)
As for susceptibility:
Resistant — 6
Susceptible — 2
As for indications:
Intolerance — 2 (out of 4)
Failure — 6 (out of 9)

II — *Improved* (13)
As for susceptibility:
Resistant — 0
Susceptible — 9
Negative — 4
As for indications:
Acute disease — 8 (out of 8)
Intolerance — 1 (out of 4)
Failure — 2 (out of 9)
Association — 2 (out of 3)

III — *Unchanged* (3)

As for susceptibility:

Resistant	1
Susceptible	1
Negative	1

As for indications:

Intolerance	1 (out of 4)
Failure	1 (out of 9)
Association	1 (out of 3)

In the cases where intolerance to chemotherapy made patients eligible for prednisone program, or whenever associated disease occurred, results herein described refer to drug effects on pulmonary tuberculosis, but not on intolerance or associated disease. Effects of prednisone on hypersensitiveness to antimicrobials were dramatic in four cases without enhancement of the tuberculous process as shown in Case 1. (Figs. 1-4)

In case of concomitant disease (two cases of asthma and one of pleurisy), the effect of prednisone was strikingly marked without detrimental repercussion on tuberculous process. [This is not the opportunity to comment the effects of prednisone in instances of asthma or intolerance, which are already well known.]

We can ascertain from the above results that bacterial susceptibility to chemotherapy had a paramount influence on the outcome of prednisone therapy in pulmonary tuberculosis as shown in the table below:

Resistant (7)

Worse	6
Improved	0
Unchanged	1

Susceptible (12)

Worse	2
Improved	9
Unchanged	1

Negative (5)

Worse	0
Improved	4
Unchanged	1

As for indications, antimicrobial drugs exerted extraordinary beneficial effects in acute instances chiefly in miliary form, where it is possible to observe a genuine resurgence of the patient. Cases 2, 3 and 4 are striking examples.

Distribution of results according to indication was as follows:

Intolerance (4)

All patients improved as for hypersensitiveness making possible the institution of a safe antimicrobial program.

As for pulmonary tuberculosis:

Worse	2
Improved	1
Unchanged	1

Acute disease (8)

Improvement	8
Unchanged	0

Associated disease (3)

All those cases where prednisone was indicated for a coexisting disease improved by the treatment (2 of asthma and one of pleurisy).

As for associated pulmonary tuberculosis:

Worse	0
Improved	2
Unchanged	1

Failure (9)

Worse	6
Improved	2
Unchanged	1

No patient exhibited any other change attributable to prednisone.

Case Reports

Case 1: M. S. L., 21, white, Brazilian, unmarried, servant, was admitted on March 3, 1958 with far advanced pulmonary tuberculosis (Fig. 1) in the second month of pregnancy. Sputum was positive, susceptible to bacteriostatics. She had been taking INH (8 mg. per kg. of body weight) and PAS (12 gm.) daily. Because of drug intolerance evidenced by severe generalized urticarious rash (even when an approach with SM was tried) it was decided to give prednisone, (15 mg. daily) for one month, 10 mg. the second and 5 mg. the third month. With the use of prednisone, she showed perfect tolerance to bacteriostatics without exacerbation of tuberculosis. Three months after combined prednisone-antimicrobial therapy she showed marked improvement (Fig. 2). There was sputum "conversion," the infiltrate resorbed and the cavities showed a significant reduction of diameter.

Case 2: F. C. S., 21, white, unmarried, servant. Admission on February 13, 1958 with far advanced pulmonary tuberculosis, miliary form, and coexisting encephalomeningitis (Fig. 3). Sputum was negative on admission although it had previously been positive. The diagnosis of tuberculous meningitis was established by clinical examination and chemical and cytological findings in the spinal fluid, as *M. tuberculosis* was not detectable. The patient had a course of INH, SM and PAS prior to admission.

Examination on entry revealed an acutely ill woman with hyperpyrexia and some mental confusion. She was placed on a therapeutic course of INH (10 mg. daily per kg. of body weight), SM (1 gm. daily) and prednisone (15 mg. daily). It was not used

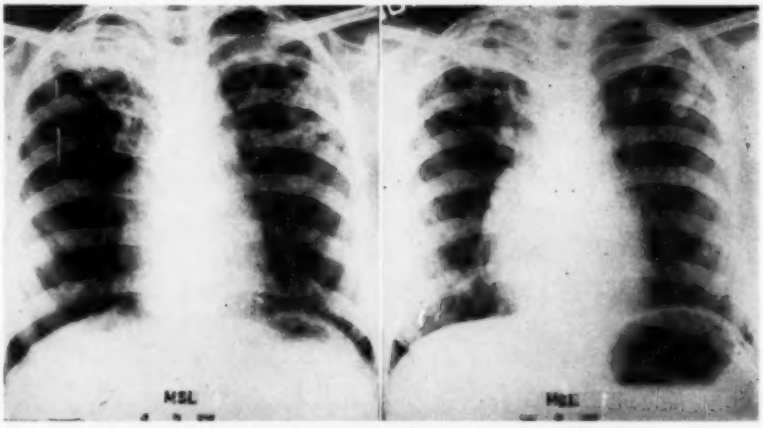

FIGURE 1 (Case 1): M. S. L., Chest roentgenogram, March 4, 1958. Infiltrative process in superior right lobe and at upper lobe at left where cavitation with fluid level is noticeable.

FIGURE 2 (Case 1): M. S. L., Chest roentgenogram, June 13, 1958 after a three months course of combined therapy showing resorption of infiltrate and significant contraction of the cavities.

the intraspinal route. During the first 15 days her condition improved significantly, the neurological picture subsided, with normal values of cerebrospinal fluid. At the end of the first month, prednisone dosage was decreased to 10 mg. daily and at third month to 5 mg. daily, maintained until August. The miliary tuberculous process showed marked regression and a chest roentgenogram taken in June, 1958 showed the miliary picture had almost completely cleared (Figure 4).

Case 3: J. C., 28, white, unmarried, servant, was admitted on March 13, 1958 with far advanced miliary pulmonary tuberculosis (Figure 5). Her general condition was poor. Hyperpyrexia, sputum positive for tubercle bacilli susceptible to antimicrobials. She was started on therapeutic regimen of INH (10 mg. daily per kg. of body weight) SM (1 gm. daily) and prednisone (15 mg. daily). After two months of treatment (Fig. 6) radiography and tomography showed normal pulmonary fields. Clinical recovery was complete.

Case 4: M. C. O., 27, mulatto, Brazilian, unmarried, servant, hospitalized on October 29, 1957, with far advanced pulmonary tuberculosis, bronchopneumonic form (Fig. 7). Her general condition was poor: high fever, sputum positive for acid-fast bacilli susceptible to antimicrobial drugs. She was placed on combined therapy of INH (10 mg. daily per kg. body weight) SM (1 gm. daily) and prednisone (15 mg. daily) the first month, 10 the second and 5 mg. the third month. Two months later she exhibited excellent condition and the x-ray films (Fig. 8) showed marked resorption of parenchymal lesions, only a regressive picture remaining at the right pulmonary bases. Sputum became negative.

Comment

Results substantiate those attained with our first series[3] and supply additional findings corroborating other writers' experience.

There is confirmatory evidence that adrenal hormones may have deleterious effects on pre-existent tuberculosis and that such enhancement of the disease may be overcome or prevented by the concurrent use of specific antimicrobials, provided that the tubercle bacilli are susceptible to these drugs. The greater number of aggravations occurred in carriers of drug-fast bacilli: of eight deteriorated cases, six were found to have such bacilli. In the improved group, none was resistant; nine were susceptible and four were negative at the beginning of prednisone regimen. Similar results are reported by Poppe et al,[11] Rizzo,[12] Warembourg and Gernez-Arieux and co-workers.[16] On the basis of this review, it would appear therefore, that chronic types of pulmonary tuberculosis, already submitted to long-term therapy harboring a bacterial population predominantly drug-resistant, are not eligible for adrenal steroid therapy. It is true, however, that in our series, two patients with chronic disease treated without favorable response, improved by the prednisone although their sputum yielded susceptible tubercle bacilli.

On the other hand, it has been observed that acute forms of pulmonary tuberculosis, chiefly miliary and caseous bronchopneumonia, represent situations where corticoid therapy evidenced most spectacular results. The effect upon symptomatology is remarkable and the patients show rapid improvement.

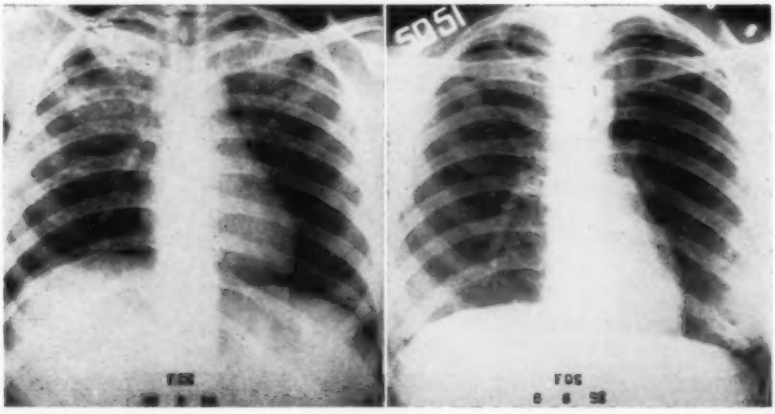

FIGURE 3 (Case 2): F. C. S., Chest roentgenogram, February 13, 1958 showing diffuse miliary process.

FIGURE 4 (Case 2): F. C. S., Chest roentgenogram, June 6, 1958, four months after the beginning of the treatment, showing almost complete resorption of the miliary process.

It has been argued[13] that it is difficult to establish whether favorable outcome of steroid and antimicrobial therapy could not be reached with chemotherapy alone. The consistent beneficial results and their rapid attainment warrant the belief that steroids at least potentiate chemotherapeutic activity. It can be said that such acute forms represent a formal indication for combined steroid-antimicrobial therapy. When intolerance to the tuberculostatic agents was present or there was another disease capable of improvement through prednisone, this drug in both contingencies afforded favorable results. The effects of prednisone upon pulmonary tuberculosis concomitantly depend on the disease features, time of previous treatment and the degree of bacterial susceptibility.

The length of prednisone course was close to three months. When evidence of deterioration was present before this term, the patients were taken off the drug. In miliary forms, the time-schedule was extended to three additional months with a maintenance dosage of 5 mg. daily. Improvement continued after the withdrawal of prednisone. Up to the present date, no relapses occurred in patients who continue under medical supervision.

The small number of cases does not yet permit definitive conclusions; these findings, however, suggest that steroid therapy already belongs to the therapeutical armamentarium of pulmonary tuberculosis, provided it is restricted to selected cases where miliary tuberculosis is an outstanding feature and that there is always concurrent specific antimicrobial coverage.

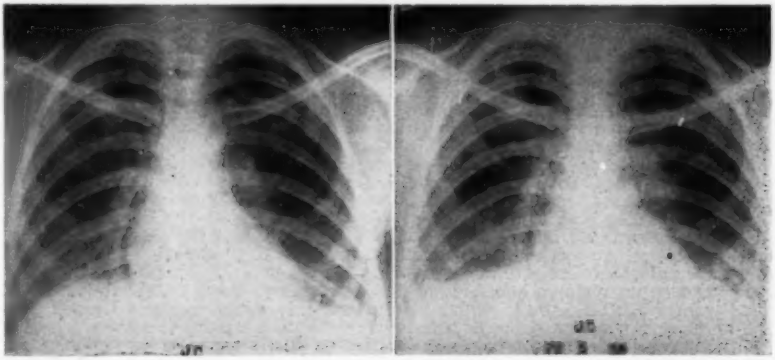

FIGURE 5 (Case 3): J. C., Chest roentgenogram, March 17, 1958 showing very fine but diffuse and extensive miliary process.

FIGURE 6 (Case 3): J. C., Chest roentgenogram, May 22, 1958, two months after she started therapy. Practically normal.

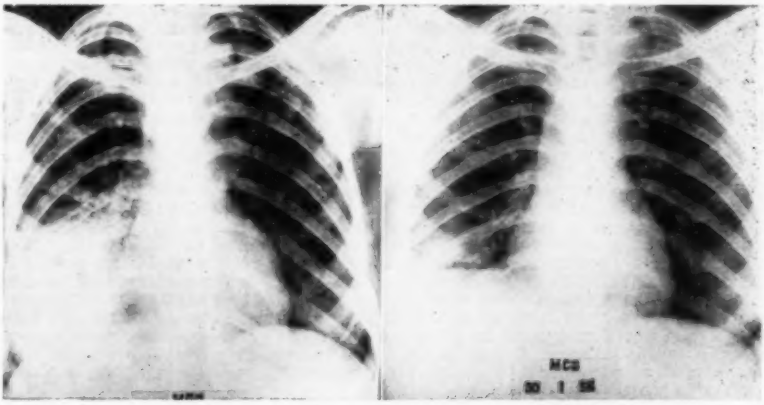

FIGURE 7 (Case 4) M. C. O., Chest roentgenogram, October 29, 1957 showing extensive bilateral lesions and a great block of condensation at right lower lobes.

FIGURE 8 (Case 4): M. C. O., Chest roentgenogram, January 30, 1958, three months after the treatment was started, showing marked improvement.

SUMMARY AND CONCLUSIONS

A series of four moderately advanced and 20 far advanced cases of pulmonary were given combined prednisone, streptomycin and isoniazid therapy. Indications were: intolerance to chemotherapeutics (acute pulmonary tuberculosis), inefficacy of long-term chemotherapy and presence of associated disease. Prednisone disclosed its powerful anti-allergic activity making possible resumption of the course of antimicrobial drugs for patients who had developed intolerance to these therapeutic agents. Chronic forms, chiefly those with drug-resistant bacilli, could not be treated with steroids. Instances with drug-fast bacilli frequently showed deterioration. Acute pulmonary tuberculosis such as miliary form and caseous bronchopneumonia vastly benefit by prednisone. In the presence of other diseases, prednisone exerts beneficial effects upon tuberculosis depending on the pathological form, period of previous treatment and the degree of susceptibility of tubercle bacilli. Three months of treatment with prednisone in a dosage of 15 mg. daily during the first month, 10 mg. daily during the second and 5 mg. daily during the third month constitute an adequate regimen. In the acute, extremely severe forms as the miliary form, this may be increased to six months, with a dosage of 5 mg. daily during the three additional months. Favorable response lasted even after withdrawal of the drug. With the last named dosage there was no untoward occurrence ascribable to the drug, with the exception of deterioration of tuberculous disease in certain cases.

RESUMEN Y CONCLUSIONES

Se administró la combinación de prednisona, estreptomicina e isoniacida a una serie de cuatro enfermos moderadamente avanzados y 20 muy avanzados de tuberculosis pulmonar.

Las indicaciones fueron por: intolerancia de agentes quimioterápicos, ineficacia de terapia a largo plazo, y presencia de enfermedad concomitante.

La prednisona demostró su poderosa acción antialérgica haciendo posible reanudar el tratamiento con drogas antimicrobianas en enfermos que ya presentaban intolerrancia a esas drogas.

Las formas crónicas, especialmente las que tenían drogo-resistencia no se pudieron tratar con esteroides. Los casos con bacilos drogo-resistentes mostraron deterioro. La tuberculosis pulmonar aguda tal como la forma miliar y la bronconeumonía tuberculosa se beneficiaron grandemente con la prednisona. En presencia de otras enfermedades la prednisona ejerce benéfica influencia sobre la tuberculosis dependiendo de la forma patológica, el período de tratamiento previo y el grado de susceptibilidad al bacilo tuberculoso.

Se considera un régimen adecuado el de tres meses proporcionando 15 mg. diarios. En las formas agudas como la miliar extremadamente severa, puede alargarse el término hasta seis meses dando 5 mg. diarios durante los segundos tres meses.

La influencia favorable persistió aún después de que la droga se suspendió. Con la dosificación mencionada al último, no hubo efectos adversos atribuibles a la droga con excepción de un deterioro de la enfermedad tuberculosa en algunos casos.

RESUMÉ

Les auteurs présentent un compte-rendu de ses études avec 24 malades traités par l'association prednisone-streptomycine-isoniazide, dont 4 presentaient une tuberculose modérement avancée et 20 la forme trés avancée. Les indications étaient les suivantes: intolerance pour les chimiothérapiques, échec de la chimiothérapie prolongée, formes pulmonaires aigües et la coexistence d'une autre maladie. La prednisone a demontré sa haute piussance anti-allergique permettant la reinstallation de la médication specifique antibacillaire dans les malades que présentaient intolerance a ces agents thérapeutiques. Les formes chroniques, surtout celles avec bacilles resistants à la chimiothérapie ne doivent pas être soumises à la corticothérapie. Dans la série des auteurs les cas resistants ont eprouvé aggravation symptomatique. Les formes aigües de tuberculose pulmonaire y compris la forme miliaire et la bronchopneumonie caséeuse sont très favorablement influencées par l'administration de la prednisone. Aussi, dans les cas de tuberculose, la présence d'une maladie susceptible détre ameliorée par l'emploi de la prednisone, justifie l'indication de cet agent. Les répercussions thérapeutiques de la prednisone sur la tuberculose sont dans la dépendence de la variéte clinique de la maladie, du traitment préalable e du degrée de sensibilité des bacilles tuberculeux. Trois mois de traitment avec la prednisone dans um régime de 15 mg par jour le premier mois, 10 mg dans le second et 5 mg dans le troisieme, constituent un programe convenable, selon confirment les resultats des auteurs. Dans les formes aigües extrémement graves, comme la forme liliaire, cette période peut être augmentée de 3 mois dans les quels on fera l'usage de 5 mg par jour. Les améliorations obtenues se sont conservées aprés la supression de la prednisone. Avec cette dose il n'y a pas eu des complications attribuables a la drogue, avec l'exception, dans quelques cas, de l'aggravation de la maladie tuberculeuse.

ZUSAMMENFASSUNG

Die Verfasser berichten über 24 mit der Kombination Prednison-Streptomycin-Isoniazid behandelte Kranke, you denen 4 eine mässing und 20 eine weit vorgeschrittene Tuberkulose aufwiesen. Die Indikationen fur diese Behandlung waren folgende: Uni-

verträglichkeit der Chemotherapie, schliessliches versagen dieser lange Zeit durchgeführten Behandlung, akute Lungenfälle und das gleichzeitige Bestehen einer anderen Krankheit. Prednison zeigt hohe antiallergische Wirksamkeit, welche die Wiederaufnahme der spezifische Therapie bei den Patienten erlaubte, die vorher Intoleranz aufwiesen. Chronische Formen besonders solche, die gagen Chemotherapie resistente Erreger zeigen, äurfen nicht mit Kortikoiden behendelt werden. In dem Krankenmaterail der Verfasser wurde bei den resistenten Fällen symptomatische Verschlenchterung festgestellt. Die akuten Formen der Lungentuberkulose, einschliesslich der Miliartuberkulose und der käsigen Bronchopneumonie werden durch die Prednisonbehandlung sehr günstig beeinflusst.

Die Anwendung dieses Mittels ist ferner berechtigt in Fällen von Tuberkulose, bei denen gleichzeitg eine andere Erkrankung besteht, die durch Prednison gebessert werden kann. Die therapeutische Wirkung des Prednisons hängt ab von der klinischen Form der Krankheit, von der vorangegagenen Behandlung und von Grad der Empfindlichkeit der Tuberkelbazillen. Gemass den von den Verfassern erzielten ist folgendes Behandlungsschema zu empfehlen: 15 mg pro Tag während des ersten Monats, 10 mg während des zweiten und 5 im dritten Monat. In besonders scheweren Fällen wie der Miliartuberkulose kam diese dreimonatige Behandlung auf weitere verlängert werden, während deren 5 mg täglich gegeben werden. Die erzielten Besserungen haben nach Absetzen des Prednisons angehalten. Bei Dosierung wurden keine dem Präparat zuzuschreibenden Komplikationen beobachtet mit Ausnahme der tuberkulösen Erkrankung in einingen Fällen.

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Experimental Repair of Tracheal Defects with Gallbladder Mucosa*,**

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Surgical treatment of malignant and certain benign lesions of the trachea may require plastic reconstruction or segmental replacement. The ideal of a rigid yet elastic tube compatible with the tracheal environment remains a problem of great challenge. In spite of outstanding success with prosthetic materials in arterial replacement there has been no satisfactory solution to tracheal reconstruction with either prosthetics or host tissues. The most promising results have utilized inert materials for support of the lumen with or without the addition of covering tissue.

In an effort to use the prosthetics only as a temporary support, investigation was undertaken of the possible adaptation of host tissues with osteogenic properties. Early experimental work of Huggins[1,2] demonstrated the specific ability of urinary tract epithelium to induce new bone formation in ectopic locations. Following the report of Rush,[3] who employed portions of urinary bladder mucosa for tracheal reconstruction, our preliminary studies demonstrated the gallbladder to have similar osteogenic potential.

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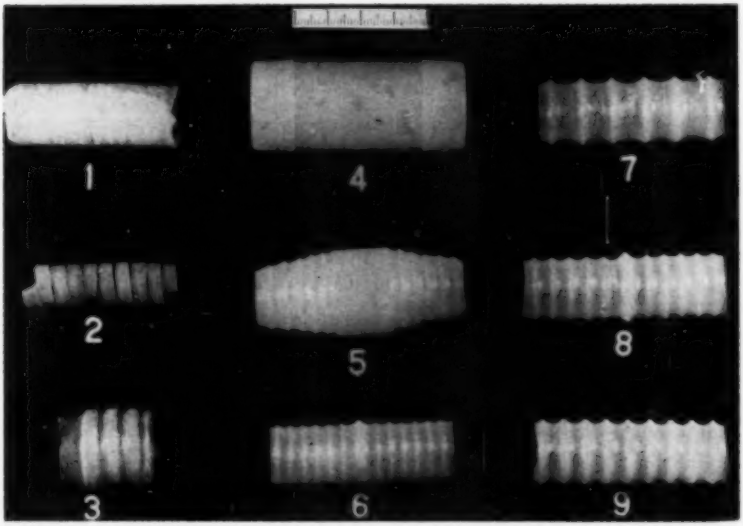

FIGURE 1: Types of tracheal prosthesis: No. 1—Ivalon and stainless steel mesh, No. 2—Nylon springs, No. 3—Nylon rings in Silastic, Nos. 4 and 5—Nylon, No. 6—Teflon, Nos. 7, 8 and 9—Polyethylene.

Methods

Healthy adult mongrel dogs weighing between 11 and 25 kg. were anesthetized with pentobarbital. All operative procedures were performed on the cervical trachea under sterile conditions. In experiments using gallbladder musoca a cholecystectomy was performed first. The seromuscular layer was stripped from the underlying biliary musoca prior to its implantation in the neck. Following the insertion of the prosthesis the epithelium was then wrapped about it, placing the musoca side out and suturing the edge of the autograft to the cut ends of the trachea with a running suture of fine catgut or wire.

In creating window defects a section one-third to two-thirds of the circumference and 5 cm. long (length of three cartilages) was excised. Segmental or sleeve resections were usually 5 to 7 cm. in length (three to four cartilages). In early experiments an attempt was made to anastomose the prosthesis end on to the cut ends of the trachea. As experience was gained and the prosthesis was improved (Fig. 1) endoluminal insertion was employed. Transfixion of the prosthesis, tracheal wall and adjacent tissues with mattress sutures of steel wire proved to be the best method for fixation.

Each experimental animal was bronchoscoped at intervals of one month or whenever indicated by obstructive symptoms. Every tissue implant was examined histologically from biopsy or necropsy specimens.

Results and Observations

Series 1. Stainless Steel Wire Mesh and Ivalon Prosthesis With or Without Gallbladder Mucosa

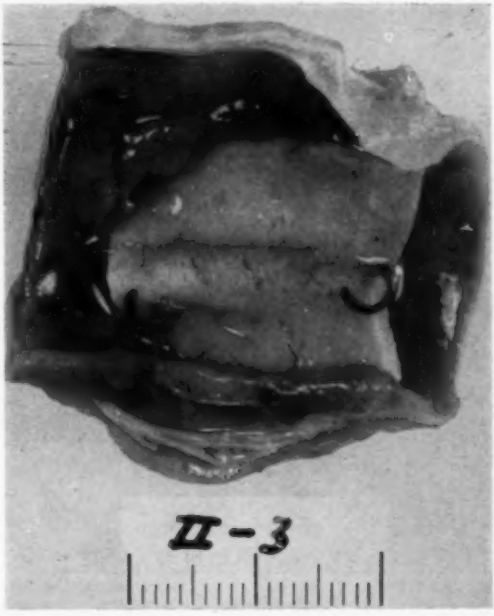

FIGURE 2: Interior view of window defect with Ivalon and stainless steel wire mesh prosthesis prolapsed into lumen.

Nine dogs were used in this series. In four animals a window defect was produced in the cervical trachea. The defect was repaired with a patch of wire mesh and Ivalon and covered with gallbladder epithelium. In each instance the patch pulled loose from the margin of the defect (Fig. 2) and prolapsed into the lumen at intervals of three to five months. Attempts to remove the prosthesis via the bronchoscope were unsuccessful and reoperation was necessary. The galbladder musoca had formed a cartilagenous bony plate over the defect which maintained the conformity of the tracheal wall (Fig. 3 and 4). The luminal surface revealed satisfactory epithelization (Fig. 5).

The remaining five animals had sleeve resection of the trachea. Each animal subsequently expired from respiratory obstruction at intervals of six days to five and one half months.

In each instance the tracheal stenosis, whether acute or chronic was due to inadequate fixation of the prosthesis. There was no evidence of healing at the junction of the prosthesis and severed end of the trachea. The prosthesis was often found to have pulled away from one or both ends of the trachea in spite of careful suturing. In the animals surviving for longer periods a ring of granulation tisue usually developed at this junction and protruded into the lumen, contributing to the cicatricial stenosis (Fig. 6).

Series II. Ivalon and Gallbladder Musoca

Four animals were used in this group. In two window defects were created and replaced with patches of compressed Ivalon (4 to 1) often supported with wire and overlayed with gallbladder mucosa. The neck in one animal was re-explored for biopsy at four weeks to determine how early osteoid or chondroid tissue would develop. This animal was subsequently sacrificed at six months. The implant area in the second dog was explored for biopsy at 60 days and the animal sacrificed at 62 days for study.

The remaining two dogs with window defects survived periods of six weeks and two months respectively. In each instance the Ivalon and/or part of the autografted mucosa had sloughed or prolapsed into the tracheal lumen with subsequent local and pulmonary sepsis and obstructive death.

Series III. Nylon Spring Prosthesis With Fascia or Gallbladder Musoca

Six dogs underwent segmental resection of the cervical trachea. Specially fabricated nylon springs varying from $\frac{3}{8}$-inch to $\frac{5}{8}$-inch in diameter were used as the prosthesis (Fig. 1). Difficulty was experienced with fixation of the springs. Although mobility of the prosthesis was excellent, there was a tendency for the spring to telescope on itself. Two springs became detached at their proximal end and a third was coughed out, resulting in an obstructive death as the residual fibrous tube collapsed. Fascia implanted about this prosthesis was slower to gain a blood supply and thus was more liable to necrosis than gallbladder musoca. Survival in this group varied from six days to two months.

Series IV. Silastic Prosthesis With or Without Gallbladder Mucosa

The results in three dogs with a prosthesis fabricated of nylon rings embedded in Silastic* (Silicone rubber) were unsatisfactory. The longest surviving animal expired

*Dow-Corning

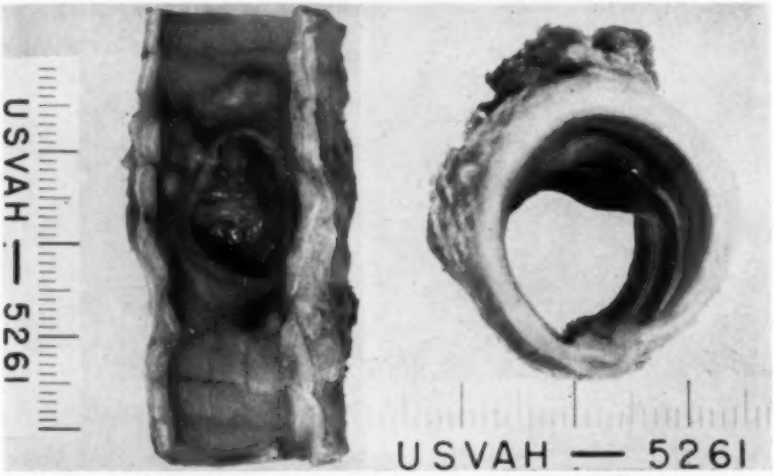

Figure 3A Figure 3B

FIGURE 3A: Luminal view of window defect at three months. Gallbladder mucosa has formed osteoplastic roof. 3B—End-on view showing maintenance of lumen and paratracheal proliferation of fibrous tissue.

at two months. Failure again resulted from inadequate fixation of the prosthesis. Malposition of either end of the prosthesis resulted in a ring of infected granulation tissue which contributed to excessive secretions and the obstructive syndrome.

Series V. Polyethylene Prosthesis With Gallbladder Mucosa

Five animals in this group had implantation of a polyethylene prosthesis. In two, a straight tube 1/16 to 1/32-inch thick and 5 to 7 cm. long was used. More recently the tube has been fabricated to simulate the trachea. Crimping of the tube tends to increase its flexibility and decrease wall thickness. The posterior wall of the tube is flattened to correspond to the membraneous trachea and avoid pressure on the esophagus. In several dogs partial esophageal obstruction resulted from too bulky a prosthesis. All of these animals have survived over six months and appear well, without stridor. Bronchoscopic examinations have revealed a clean lumen with epithelization.

Summary of Microscopic Findings

The first change of the gallbladder mucosa following this ectopic disposition was cystic dysplasia. Microscopically, a biopsy at four weeks showed papillary mucosal remnants at the base of large cystic follicles. In many areas the cystic mucous glands had ruptured and coalesced into still larger cysts (Fig. 7). Scattered islands of pink staining chondroid or osteoid material appeared to be developing in proximity to the proliferating interstitial fibroblasts (Fig. 8). At six and 10 weeks the islands of chondroid or new cartilage were better developed at the base of the cystic spaces some of which were largely evacuated of mucin.

At seven months following repair of a window defect, a cross section revealed pink staining osteoid or chondoid material growing from the cut ends of the tracheal cartilage (Fig. 9). The galbladder mucosa was still recognizable as papillary epithelium among the enormous cystic hyper-

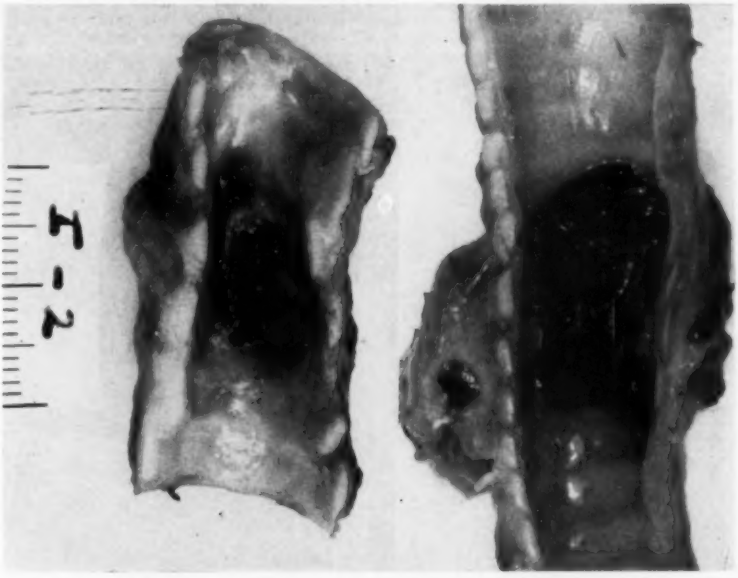

Figure 4 Figure 5

FIGURE 4: Large window defect at six months. Note excessive formation of fibrocartilagenous tissue in paratracheal area. Defect is completely filled with similar tissue.

FIGURE 5: Luminal view of fenestra defect repaired with biliary epithelium showing complete epithelization at four months.

trophy of the mucous glands. Subacute and chronic inflammatory round cells were present in the granulating tisue. New bone formation (endochondral type) is also seen in areas distinctly removed from the margins of proliferating tracheal tissue. On the luminal surface of the gallbladder patch pseudostratified metaplastic squamous epithelium had regenerated over the entire area (Fig. 10).

Discussion

Regardless of the type of tube used for the stent providing it is stable and of inert material, a fibrous pseudotrachea forms from the cut ends. The tube thus formed never gains a sufficient degree of rigidity to remain patent during respiration. The hope in using implants of tissue with known osteogenic potential such as rib or intercostal pedicle for segmental tracheal replacement is the formation of a permanent tube. With autografts capable of inducing bone formation by metaplasia of connective tissue fibroblasts, urinary or gallbladder epithelium may offer the same possibility.

Many workers[4,5] have used autografts for experimental or clinical replacement of a tracheal or bronchial defect. Bronchial autografts are ideal but their use is limited by their availability and unique clinical circumstances. Autografts of fascia, pleura and periosteum have met with limited success. Wire-supported dermal skin has proved very satisfactory in the expert hands of Gebauer.[5]

Although Rush[3] in attempting to use the urinary bladder mucosa as a sheet around a polyethylene stent noted new bone formation at 60 days, he was unable to gain surviving animals when the stent was removed at three month intervals. The majority of animals died of respiratory obstruction from marked edema in the submucosal layers.

The possibility of using an autograft initially rigid such as cartilage, bone or a tissue with osteogenic potential as periosteum has been explored by several investigators. Pressman[7] demonstrated healing of a section of decalcified bone implanted in an anterior tracheal window. The same type of implant failed as a posterior window due to lack of blood supply. Segmental replacement with a decalcified hollow bone tube was also unsatisfactory as the fibrous tube which resulted from resorption of the bone was non-rigid. Extending his earlier work, Pressman[8] reported the success of preserved dura mater and lyophilized homologous aorta in closing large tracheal defects. Using these tissues about a polyethylene tube as a stent he obtained improved healing and epithelization of the mucosal surface.

The critical problem in maintaining the tracheal lumen following creation of a large fenestration or ring defect is adequate fixation of the stent. Plastic tubes are readily available and apparently present less of a mucous barrier than metallic

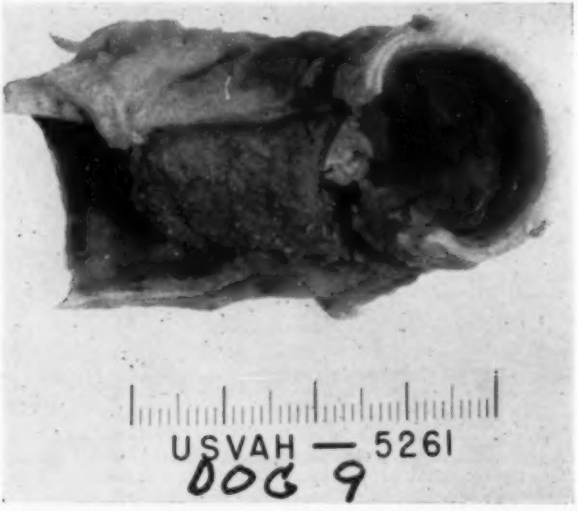

FIGURE 6: Malposition of a stainless steel wire mesh and Ivalon prosthesis. Obstructive granulations and stenosis at proximal end of implant site (2½ months).

inserts.[9] Whether a stent is used temporarily to permit healing of a non-rigid autograft or is allowed to remain as a permanent replacement, similar methods of fixation are required. The most frequent complication is migration of the stent to a subglottic position or local malposition. With excessive motion of the tube a ring of protuberant granulation tissue may form at either end. Pressman has noted that if the severed

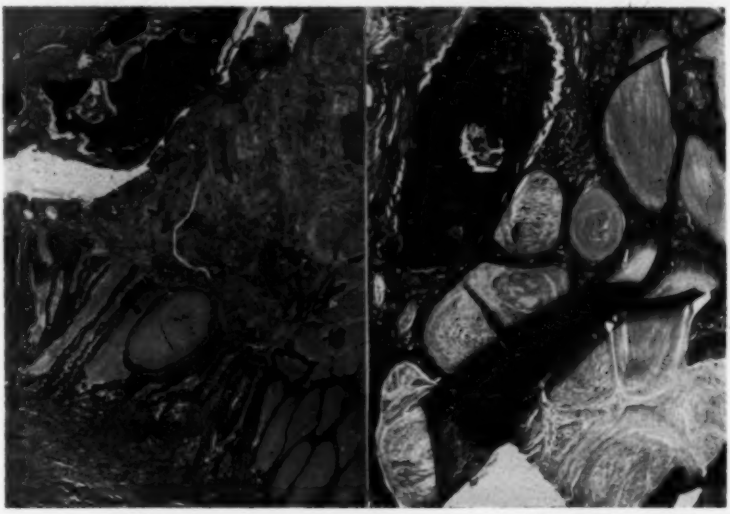

Figure 7 Figure 8

FIGURE 7: Photomicrograph of papillary hyperplasia and retention cysts of mucous glands of gallbladder mucosa. Island of new bone formation at four weeks. X 43
FIGURE 8: Photomicrograph of cytic dyplasia of mucosa. Island of osteoid or chondroid developing from subjacent fibroblasts in lamina propia at six weeks. X 400

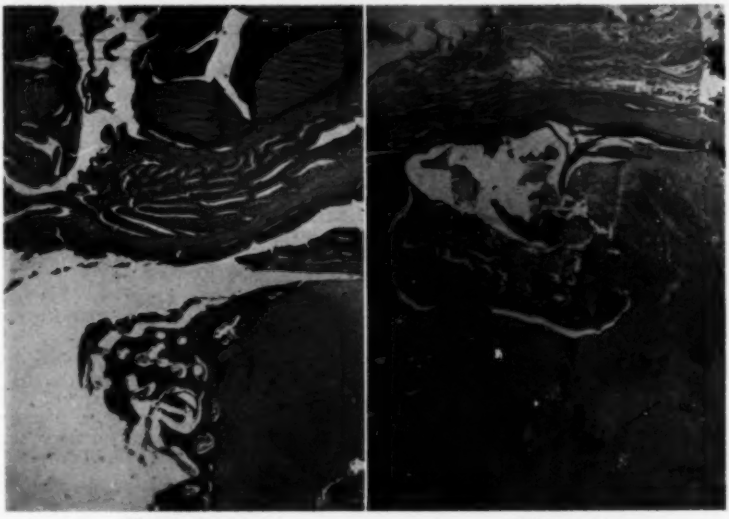

Figure 9 Figure 10

FIGURE 9: Photomicrograph of new cartilage regenerating from parent tracheal cartilage. Persistence of papillary hyperplasia and cysts of adjacent biliary mucosa at six months. X 43
FIGURE 10: Photomicrograph of regenerated pseudostratified squamous epithelium. Underlying the fibrous tissue layer is an island of metaplastic cartilage far removed from tracheal cartilage. Six months. X 43

ends of the trachea are allowed to heal to autografted tissue there is less tendency for the proliferating granulation tissue to invade the lumen.

The survival of autografted tissue would appear to depend on the success of local vascularization. With a large fenestra type defect in which it is possible to preserve the posterior third of the tracheal circumference an intrinsic blood supply is possible. In cylindrical replacement, survival of tissue implants appears to depend on establishment of a blood supply from the adjacent strap muscles. Exposure of the ectopic tissue to the bacterial flora of the tracheal lumen may jeopardize the implant survival. Although Rob and Bateman[10] were moderately successful with the clinical use of tantalum gauze covered on both sides by fascia lata, we have been unable to duplicate these results in the laboratory. The margins of the splint show no evidence of healing to the adjacent trachea and if the splint is semi-permeable the ingrowth of granulation tissue contributes to ultimate stenosis. Our best results to date have been with the straight slightly modified polyethylene tube.

In agreement with the findings of Huggins and others, we were able to identify new bone or cartilage after four weeks of implantation. Serial study up to six months reveals a progressive increase in the amount and maturity of the endochondral bone. Although these scattered islands lend support to the fibrous tube, it has not been demonstrated that such a tube is capable of complete replacement of ring defects beyond two cartilages in length. Window defects and short cylindrical defects may be successfully replaced by a variety of tissue autografts providing there is temporary support.

Perhaps the most promising application for chondrogenic autografts is the treatment of congenital tracheobronchial anomalies. A further use would be in repairing localized areas of chondromalacia resulting from pressure of adjacent vascular anomalies or benign tumors.

SUMMARY

1. New cartilage and bone formation may be consistently induced in the paratracheal area by implantation of gallbladder mucosa.

2. With the use of non-rigid tissue autografts, temporary support of the tracheal lumen with inert plastic tube stents is necessary.

3. Window defects are satisfactorily repaired with autografts of osteogenic potential. The assumption of a cartilagenous type of rigidity by the autograft permits removal of the endoluminal stent.

4. Tissue autografts with osteo or chondrogenic induction capacity offer the possibility of permanent rigid tube replacement of cylindrical tracheal defects. Such replacement has not yet been satisfactory in the absence of the stent support.

RESUMEN

1. Se puede provocar la formación de cartílago nuevo y de hueso de manera constante, mediante la implantación de mucosa de la vesícula biliar.

2. Por el uso de autoinjertos de tejidos no rígidos, se requiere soporte temporal de la luz traqueal con tubos plásticos inertes.

3. Las ventanas por defecto se reparan satisfactoriamente con autoinjertos de potencial osteogénico. Se supone que al obtenerse una rigidez del conducto de tipo cartilaginoso, se puede retirar el tubo de soporte como férula interna.

4. Los autoinjertos con capacidad para desarrollar huesos o cortílago, ogrecen la posibilidad de substitución de los tubos rígidos en caso de defectos cilíndricos traqueales.

Tal substitución no ha sido aún satisfactoria sin el uso de los soportes de apoyo.

RESUMÉ

1. La formation de nouveau cartilage et d'os peut être provoquée d'une façon valable dans la zone paratrachéale par implantation de muqueuse de vésicule biliaire.

2. Avec l'emploi d'autogreffes de tissu non rigide, un support temporaire de la lumière trachéale est nécessaire, avec un tube en plastique inerte.

3. Les altérations de la fenêtre sont réparées de façon satisfaisante avec des autogreffes à pouvoir ostéogénique. L'apparition d'une rigidité cartilagineuse de l'autogreffe permet la suppression du support endotrachéal.

4. Les autogreffes de tissus ayant un pouvoir de production ostéo ou chondrogénique offrent la possibilité de remplacer par un tube rigide permanent les altérations trachéales cylindriques. Un tel remplacement n'a pas encore été satisfaisant en l'absence d'un support solide provisoire.

ZUSAMMENFASSUNG

. Neue Knorpel- und Knochenverbände können als ganzes in den paratrachealen Bereich eingeführt werden durch Implantation von Gallenblasenschleimhaut.

2. Bei der Verwendung von nicht rigiden Gewebs-Autotransplantaten ist eine temporäre Stütze des Luftröhrenlumens erforderlich mit Stents aus stumpfem Platikrohr.

3. Gefensterte Defekte werden zufriedenstellend beseitigt durch Autotransplantate mit osteogener Potenz.

Der Zusatz einer Art knorpelförmigen Rigidität durch das Autotransplantat erlaubt die Entfernung des endotrachealen Stentzes.

4. Gewebs-Autotransplantaten mit osteo- oder chondrogenem Induktionsvermögen bieten die Möglichkeit eines ersatzes von zylindrischen Luftröhrendefekten. Solcher Ersatz war bisjetzt noch nicht befriedigend bei Fehlen einer Stütze durch Stentz.

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Effect of Pyrazinamide on Antimicrobially Active Serum Isoniazid*

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Microbiologic investigation of the prevention of emergence of mutant populations of tubercle bacilli resistant to either streptomycin or isoniazid emphasized the fact that adequate sterilizing concentrations of each of these drugs were necessary at the sites of bacterial multiplication.[1,2]

Delivery of adequate concentration of isoniazid to a patient's tubercle bacilli requires different dosages for different patients,[3] because of the wide differences in rates of isoniazid inactivation in different individuals.[3] One way to insure that all patients will maintain adequate serum levels is to increase the dosage of isoniazid.[3] Some few subjects, however, inactivate isoniazid so rapidly that dosages of 16-20 mg. isoniazid per kg. body weight are insufficient to maintain adequate antimicrobially active isoniazid serum levels.[3] In these patients, high dosage of isoniazid plus the concomitant administration of aromatic amines preventing the rapid inactivation of isoniazid are necessary in order to attain the minimum serum level consistent with adequate antibacterial effect.[3,4] The decrease in the rate of metabolic alteration of isoniazid by these drugs has been attributed to competition for the biochemical process of acetylation, which is one of the major pathways of isoniazid inactivation.[5,6]

Thus far, two drugs have been shown to decrease the metabolic alteration of isoniazid and increase the serum levels of antimicrobially active drug: para-aminosalicylic acid and para-aminobenzoic acid.[3] Recently, in a report coming from Japan,[7] a third drug, pyrazinamide, was stated to decrease the rate of metabolic alteration of isoniazid. In order to establish whether the simultaneous administration of pyrazinamide with isoniazid increase the antimicrobially active serum moiety of this drug, the serum isoniazid levels achieved by tuberculous patients on isoniazid alone were compared to those achieved when isoniazid and pyrazinamide were administered together. The purpose of this presentation is to report the results of this experiment.

Methods and Material

Nineteen adult tuberculous patients were selected for this study: nine rapid isoniazid inactivators and 10 slow isoniazid inactivators.** For two days prior to the initial test these patients received 8 mg. isoniazid per kg. body weight twice daily. No other drugs were given. On the day of

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**A rapid isoniazid inactivator was defined as a tuberculous patient who, six hours after ingesting a single loading dose of 4 mg. isoniazid per kg. body weight, had a serum level of antimicrobially active isoniazid of less than 0.4 mcg. per ml. serum; a slow isoniazid inactivator was defined as a patient who, six hours after the administration of 4 mg. isoniazid per kg. body weight, had a serum level of antimicrobially active isoniazid of 0.4 mcg./ml. or more.

the test, a single oral dose of isoniazid, 8 mg. per kg. body weight, was administered. The total dose given ranged from 200 - 600 mg. Venous blood samples for the determination of the serum level of antimicrobially active isoniazid were obtained six hours after the administration of the loading dose of isoniazid.

Repeat studies on each of these 19 patients were performed under the same conditions after administering the same amounts of isoniazid and 1.5 gm. pyrazinamide daily for two days. The loading dose on the day of the test was 8 mg. isoniazid per kg. body weight and 0.5 gm. pyrazinamide.

The microbiologic assay for antimicrobially active isoniazid is based on the phenomenon of loss of acid-fastness by tubercle bacilli exposed to the action of a sufficient concentration of isoniazid.[8] The loss of acid-fastness is specific for isoniazid as no other known antimicrobial agent has this effect on tubercle bacilli.[8]

The microbiologic assay for antimicrobially active serum isoniazid was peformed as follows:

1. *Preparation of serum samples:* Eight ml. of venous blood were collected from patients six hours following an oral loading dose, equivalent to half the daily dosage of isoniazid. The blood specimens were allowed to clot at room temperature, then were centrifuged, and the supernatant serum was transferred to sterile tubes and stored in the refrigerator.

TABLE 1 — ISONIAZID SERUM LEVELS SIX HOURS AFTER A LOADING DOSE OF 8 mg. ISONIAZID PER KG. BODY WEIGHT WITHOUT AND WITH 0.5 gm. OF PYRAZINAMIDE*

Patient	Isoniazid level without pyrazinamide**	Isoniazid level with pyrazinamide**
1.	0.2 mcg/ml	0.2 mcg/ml
2.	0.3 mcg/ml	0.4 mcg/ml
3.	0.3 mcg/ml	0.3 mcg/ml
4.	0.4 mcg/ml	0.6 mcg/ml
5.	0.4 mcg/ml	0.4 mcg/ml
6.	0.4 mcg/ml	0.4 mcg/ml
7.	0.4 mcg/ml	0.6 mcg/ml
8.	0.4 mcg/ml	0.6 mcg/ml
9.	0.6 mcg/ml	0.8 mcg/ml
10.	0.8 mcg/ml	0.8 mcg/ml
11.	0.8 mcg/ml	0.8 mcg/ml
12.	0.8 mcg/ml	0.8 mcg/ml
13.	1.2 mcg/ml	1.2 mcg/ml
14.	1.2 mcg/ml	1.6 mcg/ml
15.	3.2 mcg/ml	3.2 mcg/ml
16.	4.8 mcg/ml	6.4 mcg/ml
17.	4.8 mcg/ml	4.8 mcg/ml
18.	6.4 mcg/ml	6.4 mcg/ml
19.	6.4 mcg/ml	4.8 mcg/ml

*Patients received 16 mg. isoniazid per kg. body weight without or with 1.5 gm. pyrazinamide daily for two days prior to the test.

**Six hour level — blood was withdrawn six hours after the administration of the loading dose.

Patients No. 1 - 9 were rapid inactivators; patients No. 11 - 19 were slow inactivators of isoniazid.

2. *Inoculum:* The inoculum used was six to seven day-old culture of an isoniazid-susceptible, streptomycin-resistant (10 mcg./ml.) strain of *Mycobacterium tuberculosis,* (H37RvS-RSM), cultivated in Tween^{R} 80-albumin Standard Transfer Medium.[8]

3. *Test medium:* An oleic acid-albumin medium was used.

4. *Method of performing the assay:* One ml. of serum was distributed by serial twofold tube dilution in seven tubes containing 2.5 ml. of the test medium seeded with 0.1 ml. inoculum. The final serum dilutions ranged from 1:5 dilution in tube No. 1 to 1:320 dilution in tube No. 7. Standard controls containing known concentrations of isoniazid (0.0, 0.02, 0.04, 0.08) and the same inoculum were included with each set of determinations. The inoculated tubes and the standard controls were incubated for five to seven days at 36° C. Ziehl-Neelsen stained smears were made from a loopful of contents of each tube and examined for complete or partial loss of acid-fastness.[9]

Under these conditions, the controls consistently showed partial to complete loss of acid-fastness at an isoniazid concentration of 0.04 mcg/ml and complete loss at 0.08 mcg. of isoniazid per ml. The standard deviation of the results of 50 consecutive microbiologic assay tests with known concentrations of isoniazid provided an estimation of the accuracy of the microbiologic assay method: ±20 per cent.[2]

The concentration of antimicrobially active isoniazid in unknown specimens was estimated accordingly as follows:

	isoniazid mcg./ml. serum
No loss of acid-fastness at 1:5 dilution	less than 0.2
Partial loss of acid-fastness at 1:5 dilution	0.2
Complete loss at 1:5, none at 1:10 dilution	0.3
Partial loss of acid-fastness at 1:10 dilution	0.4
Complete loss at 1:10, none at 1:20 dilution	0.6
Partial loss of acid-fastness at 1:20 dilution	0.8
Complete loss at 1:20, none at 1:40 dilution	1.2
Partial loss of acid-fastness at 1:40 dilution	1.6
Complete loss at 1:40, none at 1:80 dilution	2.4
Partial loss of acid-fastness at 1:80 dilution	3.2
Complete loss at 1:80, none at 1:160 dilution	4.8
Partial loss of acid-fastness at 1:160 dilution	6.4
Complete loss at 1:160, none at 1:320 dilution	9.6
Partial loss of acid-fastness at 1:320 dilution	12.8
Complete loss of acid-fastness at 1:320 dilution	more than 12.8

Using these criteria, isoniazid serum levels studies at six hours after a loading dose of 4 mg. isoniazid per kg. body weight were repeated once on 163 patients after one day to six months intervals.[2] The standard deviation of the second determination of the isoniazid serum level from the first determination on each patient throughout the range 0.2 mcg. to 4.8 mcg. isoniazid per ml. serum was ± 28 per cent.

Results

The comparison of the serum levels of antimicrobially active isoniazid achieved by 19 tuberculous patients after the administration of 8 mg. per kg. body weight loading dose of isoniazid with and without pyrazinamide did not reveal a difference between the paired levels, greater than the error inherent in the technical procedure (Table 1).

Comment

Previous investigations have shown a wide variation in the rate of metabolic alteration of isoniazid from person to person, but a relatively constant rate in any one individual.[2] Thus the influence of other drugs on the serum level of antimicrobially active isoniazid could be tested by performing the tests on the same patients acting as their own controls.[2]

The biologic phenomenon of one drug raising the blood level of another drug is not uncommon. Results of previous studies demonstrated that concurrent administration of para-aminosalicylic acid with isoniazid raised the serum concentration of active isoniazid when measured six hours after the ingestion of the loading dose.[2] The delivery of higher concentrations of isoniazid to multiplying tubercle bacilli achieved by this action of para-aminosalicylic acid may be responsible in part for the superiority of the para-aminosalicylic acid-isoniazid regimen over isoniazid alone.

The purpose of this study was to find out whether pyrazinamide, another antimycobacterial drug, had a similar effect on serum concentrations of microbiologically active isoniazid. The results obtained in 19 tuberculous patients clearly demonstrated that pyrazinamide when administered simultaneously with isoniazid did not influence the serum level of that moiety of the drug which has the therapeutic action. This was shown to be so for the rapid, as well as for the slow inactivator.

SUMMARY

A study was performed in order to establish whether the simultaneous administration of pyrazinamide with isoniazid increased the antimicrobially active moiety of isoniazid in serum of patients with tuberculosis six hours after ingesting the drugs. No effect on the serum levels of microbiologically active isoniazid was noted in 19 patients: The paired levels achieved on isoniazid alone and on isoniazid-pyrazinamide were essentially identical.

RESUMEN

Se llevó a cabo un estudio para establecer si la administración simultánea de pirazinamida con isoniacida aumenta la parte activa de la isoniacida en el suerdo de los enfermos de tuberculosis seis hors después de la ingestión de las drogas.

No se notó efecto sobre los niveles del suero de isoniacida microbiológicamente activa en 19 enfermos: los niveles pareados logrados en isoniacida sola y en el caso de isoniacida-pirazinamida, fueron esencialmente idénticos.

ZUSAMMENFASSUNG

Es wurde eine Untersuchung vorgenommen, um festzustellen, ob die gleichzeitige Verwendung von Pyrazinamid in Verbindung mit INH das anitmikrobielle Vermögen von INH im Serum bei Patienten mit Tuberkulose erhöhte 6 Stunden nach Einnahme des Mittels. Bei 19 Patienten wurde kein Einfluß auf die Serumwerte hinsichtlich der mikrobiellen Aktivität des INH festgestellt; die gepaarten Werte von INH allein und von INH mit Pyrazinamid waren im wesentlichen identisch.

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Clinical Experience with Tests for Pulmonary Function: Review of 100 Consecutive Cases*

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Much work has been done to establish normal values for use in the laboratory assessment of pulmonary function. Deviations from predicted normal values occur in many pulmonary and nonpulmonary diseases.[1-4] Reports of experiences in clinical practice have been few and usually they have been restricted to a discussion of technic or of specific clinical problems.[5-7] It was felt that it would be of interest to clinicians and physiologists alike to review the records of 100 consecutive patients referred for testing of pulmonary function in an attempt to assess the reasons for the patient's referral to the laboratory, the physiologic abnormalities observed and the usefulness to the referring physician of the information obtained.

Methods

Measurements of volume of lungs, maximal breathing capacity, and indexes of retarded alveolar ventilation were obtained by technics previously described.[8,9] Rate of flow of air during a maximally rapid and deep expiration was evaluated by the technic of Leuallen and Fowler.[10] Arterial oxygen saturation was calculated from a continuous photokymographic recording of a double scale oximeter earpiece with the patient breathing room air and 100 per cent oxygen both before and during exercise.

The physiologic data obtained from the examination of 100 consecutive patients were reviewed and the clinical record of each patient was examined.

Results

Many diseases are represented in the series (Table 1). The diagnoses listed are those arrived at by the clinician after all investigations were completed. Of the 100 patients referred to the laboratory, 61 suffered from emphysema, asthmatic bronchitis, or episodic asthma; 11 suffered from either pulmonary fibrosis alone or fibrosis complicated by a varying degree of emphysema, and 6 had normal results to tests of pulmonary function and were given a final diagnosis of functional dyspnea. The remaining 22 patients had a variety of diseases.

Patients were referred for studies of function either for quantitative assessment of pulmonary function or for diagnostic assistance. By far the most frequent reason for referral was for quantitation, as previously noted by Morgan and Yore.[11] Seventy-seven patients sent to the laboratory had clinically obvious pulmonary insufficiency. Twenty-five patients

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TABLE 1—FINAL CLINICAL DIAGNOSIS GIVEN 100 CONSECUTIVE PATIENTS REFERRED FOR STUDIES OF PULMONARY FUNCTION

	Patients
Emphysema	42
Asthmatic bronchitis and asthma	19
Pulmonary fibrosis	9
Pulmonary fibrosis and emphysema	2
Functional dyspnea	6
Pneumonectomy	3
Bronchiectasis	3
Skeletal deformity of the thorax	3
Bronchogenic carcinoma	2
Obesity	2
Miscellaneous*	9

*Scleroderma, silicotuberculosis, sarcoidosis, cystic disease of the lung, paralyzed diaphragm, ruptured bronchus, chylothorax, angina, granulomatous disease of the lung.

had been studied previously in the laboratory and were referred for follow-up studies.

Seventeen patients had preoperative evaluation of pulmonary function (table 2). In 12 cases a thoracic surgical procedure was contemplated.

TABLE 2—PREOPERATIVE EVALUATION OF 17 PATIENTS REFERRED FOR STUDIES OF PULMONARY FUNCTION

		Patients
Type of operation contemplated		
Thoracic		12
Nonthoracic		5
Cause of pulmonary insufficiency		
Asthmatic bronchitis and emphysema		8
Bronchiectasis		3
Other conditions*		6
Influence of preoperative studies of pulmonary function		
Operation performed		9
Operation not performed		8
Inoperable because of pulmonary insufficiency	3	
Inoperable for other reasons	5	

*Pulmonary fibrosis, bronchogenic carcinoma, chylothorax, silicotuberculosis, skeletal deformity, granulomatous disease.

Obstructive ventilatory insufficiency was the commonest pattern of abnormality observed preoperatively, but only three patients were not operated on because of poor function. Five other patients were inoperable for other reasons, the chief reason being evidence of metastatic malignant disase. Each of the 17 patients represented a difficult problem in surgical management and was sent to the laboratory for possible assistance. Tests for pulmonary function indicated better function than was anticipated from clinical assessment in the patients who subsequently underwent surgical measures.

The effect of an aerosol bronchodilator drug was requested for 83 patients but it was never the principal reason for referral to the laboratory. Considerable improvement followed in 38 of the 83 patients; improvement was questionable in 22. Table 3 shows that the results of this test do influence the use of aerosol bronchodilator drugs in the subsequent treatment of the patient.

TABLE 3—EFFECT OF AEROSAL-BRONCHODILATOR TEST IN DETERMINING TREATMENT FOR 83 PATIENTS REFERRED FOR STUDIES OF PULMONARY FUNCTION

Objective response to test	Patients tested	Patients treated with aerosol
Marked	38	34
Questionable	22	13
None	23	6

Twenty-three patients were referred primarily for diagnostic assistance. The diagnosis tentatively entertained prior to the tests was confirmed in six cases, and altered in 14 (table 4). In two of three cases in which the clinical diagnosis was obscure, abnormalities of tests were contributing factors in clarification.

TABLE 4—DIAGNOSTIC AID AFFORDED 23 PATIENTS REFERRED FOR STUDIES OF PULMONARY FUNCTION

		Patients
Clinical diagnosis confirmed		6
Clinical diagnosis altered		14
Erroneous diagnosis before tests		
Emphysema	5	
Left ventricular failure	4	
Others	5	
Corrected diagnosis after tests		
Pulmonary fibrosis	3	
Asthmatic bronchitis	4	
Functional dyspnea	3	
Emphysema	2	
Others	2	
Clinical diagnosis obscure before tests		3
Aided by results	2*	
Unaided by results	1	

*Pulmonary fibrosis was the final clinical diagnosis in both patients.

Comment

The majority of the 100 patients studied suffered from obstructive ventilatory insufficiency severe enough to allow ready recognition of their pulmonary disability by clinical appraisal alone. Emphysema, asthmatic bronchitis and episodic asthma alone or in combination were responsible for the preponderance of this form of pulmonary insufficiency.

Obstructive ventilatory insufficiency was characterized by the presence in varying combinations of increased residual volume, decreased vital and maximal breathing capacity, decreased rate of flow of a maximally rapid and deep expiration, and evidence of retarded alveolar ventilation as shown by abnormal indexes of pulmonary nitrogen clearance. In some patients with emphysema and bronchospastic disease, the extent of impairment of function was out of proportion to the patient's complaints. The values of arterial oxygen saturation at rest and after exercise also were useful factors in these patients. The occurrence of peripheral arterial hypoxemia of moderate degree during rest or during exercise was observed in some patients in whom cyanosis was not apparent. In accordance with the findings of Miller and associates,[12] five patients with chronic cor pulmonale and emphysema had peripheral arterial oxygen desaturation at rest or to an appreciable degree during exercise.

Reversibility of airway obstruction was tested by the effects of an aerosol bronchodilator drug on vital capacity, maximal breathing capacity and rate of forced expiratory flow. The results influenced the subsequent management of patients as shown by the correlation between magnitude of the measured response and the frequency of use of an aerosol bronchodilator as a therapeutic agent. Six patients, three of whom had pulmonary fibrosis and might not have been expected to respond, reported such marked symptomatic improvement that a bronchodilator was prescribed even though the tests did not indicate that it was effective.

At the Mayo Clinic it is not the usual practice to refer to the laboratory all patients with impaired pulmonary function for whom a surgical procedure is contemplated. In the presence of severe disease, however, results of tests for function are used to help estimate a patient's ability to withstand a surgical procedure, especially if resection of functioning lung tissue is contemplated. Three of 12 patients were considered unsuitable for thoracic operation because of obstructive pulmonary insufficiency. The other nine patients who finally underwent thoracic surgical procedures did well postoperatively. Less respiratory reserve is required for extrapulmonary procedures, whether in the thorax or outside of it, and no patient in this category was refused operation on the basis of abnormal results of the tests for pulmonary function. They, too, had satisfactory postoperative courses.

The restrictive type of ventilatory insufficiency was more difficult to recognize clinically than was the obstructive type. This abnormality is characterized by reduced lung volumes without evidence of impaired ventilation. Significant arterial hypoxemia was frequently observed in patients in whom cyanosis had not been noted. The inference that hypoxemia, especially with exercise, was attributable to a decreased oxygen-diffusing capacity, as in the syndrome of alveolocapillary block, was based on the absence of evidence of veno-arterial vascular shunts or regional hypoventilation. According to the criteria established by Austrian and associates[13], the presence of alveolocapillary block can be established only by laboratory methods. Its recognition aids greatly in understanding the impairment from which the patient suffers even though it is not in itself an acceptable diagnosis.

The insidious onset of the symptoms and varying clinical courses of the patients made the diagnosis of pulmonary fibrosis the most commonly overlooked in the group studied, especially when the thoracic roentgenograms failed to show a definitive abnormality. While clinical evidence of disturbed pulmonary function was implied in the request for laboratory studies, the principal problem in cases of pulmonary fibrosis was uncertainty of diagnosis. The establishment of this diagnosis, often accomplished by exclusion of other causes of symptoms, was aided materially by the results of studies of pulmonary function. In two patients, the presence of diminished lung volumes was the only evidence of abnormalities sufficient to cause the dyspnea of which they complained. The clinical diagnosis remained obscure until these results were obtained. Three of the 11 patients who suffered from pulmonary fibrosis had erroneous diagnoses made before studies of pulmonary function were carried out.

Asthmatic breathing in patients with systemic arterial hypertension led to a diagnosis of left ventricular failure in four patients shown later to have asthmatic bronchitis. Increased residual volume, considerable expiratory slowing and retarded clearance of pulmonary nitrogen indicated primary bronchopulmonary disease rather than pulmonary vascular congestion.

In the six cases of functional dyspnea, essentially normal results for tests of pulmonary function gave substantial assistance in diagnosis. In one instance the tests were specifically ordered and the results used to reassure the patient that pulmonary function was normal.

In two grossly obese patients reduced vital capacity and arterial hypoxemia were present without evidence of obstruction of the airway. These abnormalities were considered secondary to obesity in which alveolar hypoventilation is now a well-recognized entity.

Distinguishing secondary polycythemia from polycythemia vera is occasionally difficult and assistance may be obtained by the demonstration of peripheral arterial oxygen desaturation and other evidence of pulmonary disease. No patients presenting this problem were encountered in this series, but there were six patients with polycythemia secondary to pulmonary disease.

SUMMARY

The records of 100 consecutive patients referred for tests of pulmonary function have been reviewed. The most frequent reason for referral was to obtain a quantitative assessment of pulmonary function. Diagnostic aid was sought in only 23 instances.

Obstructive ventilatory insufficiency was the commonest abnormality encountered and was observed in 61 patients having emphysema, asthmatic bronchitis, or episodic asthma alone or in varying combinations. Improvement indicated by ventilatory tests after the use of a nebulized bronchodilator drug had a definite influence on use of the drug as a therapeutic agent.

Restrictive ventilatory insufficiency due to pulmonary fibrosis was more difficult to identify clinically. Arterial hypoxemia of significant degree was frequently observed in patients in whom cyanosis had not been noted. Preoperative evaluation of pulmonary function by laboratory methods was of value in patients with greatly reduced respiratory reserve, especially when pulmonary resection was contemplated.

RESUMEN

Se han revisado los experientes de 100 enfermos consecutivos enviados para pruebas funcionales pulmonares. La causa mas frecuente para solicitar el estudio, fué para obtener estimación cuantitativa de la funcinón pulmonar. Como ayuda para el diagnóstico sólo se solicitaron en 23 casos.

La insuficiencia ventilatoria obstructiva, fué la anormalidad más frecuentemente encontrada y se observó en ól enfermos de enfisema, bronquitis asmática o asma episódica sola o en combinaciones varias. La mejoría indicada por las pruebas ventilatorias después del uso de una droga broncodilatadora nebulizada tiene una influencia definida sobre el uso de la droga como agento terapéutico.

La insuficiencia respiratoria restrictiva debida a fibrosis pulmonar, fué más difícil de identificar clínicamente.

La hipoxemia arterial de grado significante fué menos a menudo observada en enfermos en los que la cianosis no se había notado.

La estimación postoperatoria de la función pulmonar por los métodos de laboratorio fué de valor en los enfermos con reserva respiratoria grandemente reducida especialmente cuando se proyectaban resecciones pulmonares.

RESUMÉ

Les dossiers de 100 malades examinés consécutivement ont été étudiés au point de vue des tests de la fonction pulmonaire. Le but le plus fréquent de ce contrôle avait été d'obtenir une estimation quantitative de la fonction pulmonaire. Ce n'est que dans 23 cas seulement que cette recherche donna des résultats valables au point de vue du diagnostic.

L'insuffisance ventilatoire obstructive fut l'anomalie la plus communément rencontrée, elle fut observée chez 61 malades, atteints d'emphysème, de bronchopathie d'origine asthmatique ou d'asthme épisodique ou en diverses associations. L'amélioration démontrée par les tests ventilatoires après emploi de produit bronchodilatatuer en aérosol eut une influence déterminée sur l'emploi du produit comme agent thérapeutique.

L'insuffisance ventilatoire restrictive due à la fibrose pulmonaire fut plus difficile à identifier cliniquement. Une importante hypoxémie artérielle a été fréquement observée chez des malades pour lesquels il n'avait pas été noté de cyanose. L'évaluation pré-opératoire de la fonction pulmonaire par les méthodes de laboratoire se montre un examen de valeur chez les malades qui avaient une réserve respiratoire fortement réduite, particulièrement quand on ut à envisager une résection pulmonaire.

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BCG Vaccination of Student Nurses: A Ten Year Experience*

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Introduction

Although BCG vaccination of humans has been utilized since 1921, it was not until 1945 that general interest in its use was aroused in the United States. In 1948, a BCG program was organized at The Brooklyn Hospital for students admitted to training in the School of Nursing. Between 1948 and 1958, tuberculin negative student nurses were given BCG vaccination.

During the 10 year period 1948-1958, important new concepts have evolved related to tuberculosis case finding, prophylaxis, and treatment. These require an evaluation of the vaccination procedure at the present time and in the light of present knowledge. The rationale of the BCG vaccination procedures has been confused by the experiences and divergent opinions of highly qualified and experienced workers in the field for they have differed greatly concerning the value of the procedure.

Because of this lack of general agreement as to the value of BCG and because of recent developments directly related to tuberculosis, prophylaxis, detection, and treatment, our experience of 10 years with a BCG program has been reviewed.

Methods and Material

A total of 494 student nurses were admitted to The Brooklyn Hospital School of Nursing between 1948-1958. Each student health record was carefully reviewed and the data recorded. On admission, every student was given a tuberculin skin test. BCG vaccination was then routinely given to the student nurses who showed tuberculin negative reactions. The tuberculin skin test was then repeated two months after the BCG was administered. Those who were not converted from tuberculin negative to positive by a single BCG administration were not revaccinated.

All students in the School of Nursing were followed with frequent chest roentgenograms for the detection of pulmonary tuberculosis during their training. Most of them had photoroentgenograms of the chest every three months while on the general hospital wards. In the senior year, the students were given special instruction for two months in tuberculosis nursing at an affiliated tuberculosis institution. An additional chest x-ray film and tuberculin skin tests were done both before and after their affiliation.

Findings

Of the 494 students admitted to nurses training between 1948-1958, 350 (70 per cent) were found to be initially tuberculin negative. The large number of tuberculin negative reactors was not unexpected and

*The Brooklyn Hospital.

were the primary concern of the BCG program as far as prophylaxis was concerned. Our tuberculosis case finding technique consisted of frequent chest x-ray films.

On admission to training, only six of the 494 students gave a history of having lived with a known case of tuberculosis. Five of these had initially positive tuberculin skin reactions.

Of those found to be tuberculin negative on admission to the school, 318 were given BCG. When tuberculin skin tests were repeated two months later, 234 (more than 73 per cent) had become tuberculin positive. The ability of one administration to convert a negative to a positive tuberculin skin reaction, varied considerably from time to time. In one class, a 100 per cent conversion rate was noted. In another class the conversion rate was as low as 55 per cent. This may have been due to variation in procedure or in the potency of the culture which was routinely obtained from the New York State Department of Health.

We were surprised to find that 71 students of the 234 had reverted to their tuberculin *negative* status on admission to tuberculosis affiliation training two years later. Thus 30 per cent of the students who were intially tuberculin negative and who had been successfully vaccinated lost their "sensitivity" and reverted to tuberculin negative status after a period of about two years.

The failure to convert 84 of the 318 tuberculin negative reactors with one BCG administration represented a failure rate of 26 per cent. However, it was found that on admission to the tuberculosis affiliation two years later, 52 (60 per cent) of the 84 students in this group were tuberculin positive. It was not clear whether these findings represent delayed tuberculin positive response to the BCG vaccination or whether some of these conversions may have represented infection due to exposure to active disease. As no tuberculin test was done between two months and two years following the BCG, this point cannot be determined. However, it emphasized one of the difficulties encountered when BCG is given. The tuberculin skin test is of little value for the detection of exposure to tuberculosis in those successfully sensitized with BCG.

Of the students who entered tuberculosis nursing with negative tuberculin reactions, 29 were found to have become tuberculin positive at the end of their training period. As chest x-ray films showed no demonstrable disease, no treatment was given for this presumed tuberculosis infection. It was noted that of these 29 students, 25 had been initially tuberculin negative. Twenty one had been converted to tuberculin positive by BCG and had spontaneously reverted to tuberculin negative status. This indicated the need for more frequent tuberculin testing and revaccination if the benefits of BCG sensitization were to be expected during the period of maximum exposure, i.e. while on tuberculosis affiliation training.

Discussion

Decreased exposure due to the advent of effective anti-tuberculous treatment has necessitated a re-evaluation of the value of vaccination programs such as the one described in this study. In addition, it is obvious that in 1959, we must be concerned with the "radiation hazard," a known phenomenon which was not considered significant under ordinary living conditions of 10 years ago. For example, reliance upon

frequent photoroentgenograms of the chest as a case finding procedure may result in as many as 15 separate exposures in a three year period. It is known that the photoroentgenogram may give almost eight times the radiation necessary for an ordinary chest x-ray film. In such cases a radiation exposure equivalent to 120 ordinary chest x-ray film exposures might be administered in this period of time.

Utilizing only the chest x-ray film as a means of indicating the presence of tuberculous infection has been criticized. Many foci of infection may occur other than in the lungs. Even tuberculosis of the lungs might not be detected in a chest film unless such lesions become large and dense enough to cause x-ray shadows.

Two years after successful BCG administration, 30 per cent of the student nurses were found to have reverted to their original tuberculin negative status. It appears that whatever protective immunizing benefits might be derived from the BCG vaccination are only short lived in a considerable number of cases. These students in effect received maximum protective benefits during their first six months of general nursing training when excessive exposure was highly unlikely. It was quite apparent that to be consistent in our program, there was a need for readministration of BCG.

However, omitting this led to some revealing facts. It was found that just before the special tuberculosis training period, 45 per cent of all of the students were tuberculin negative. Among this group, 29 students (18 per cent) converted to tuberculin positive during this two month period. This seemed to indicate an unusually high conversion rate in a short period of time and led to the conclusion that adequate protection was not being provided during the two months of tuberculosis nursing training. Our omission of BCG therefore led to the discovery of a high incidence of tuberculosis infection in an institution where special precautions should be taken. This incident demonstrates the value of the tuberculin test in indicating breakdowns in technique and sources of exposure. The need for corrective measures was obvious and would have been completely overlooked if we had consistently readministered BCG and kept all students continually tuberculin positive.

A considerable portion of the students vaccinated with BCG had minor reactions, such as inflammation at the site of injection and tender axillary lymph nodes. At least one had small granulomatous lesions at the site of the multiple needle injection. These subsided after many months. However, most of the reactions have been so moderate that adequate records do not exist of their incidence.

It is not our purpose to enter into the many arguments pro and con concerning the *value* of BCG. Because we have far too few cases and we have no control group, the value of tuberculosis prevention by BCG cannot be determined by the present study. We believe that effective treatment and early detection of tuberculosis have contributed greatly to the decreased exposure of student nurses to unsuspected sources of infection. However, our BCG program has been reviewed and found to have many disadvantages. Chief among these has been the obvious loss of value of tuberculin skin reactions as a case finding technique. In addition, we have demonstrated that the supposed immunity conferred by BCG administration and manifested by conversion of tuberculin negative to tuberculin positive reactors is not of long duration in a significant number of cases. Re-administration would be required repeatedly to maintain a program consistent with its own principles, that is to keep all of the students tuberculin positive at all times.

Another objection of real importance today is the fact that if BCG is given properly and tuberculin skin tests are therefore kept positive, there is no way of discovering early tuberculosis except by the use of frequent chest x-ray films. The disadvantages inherent in the extent to which this must be employed, especially if photoroentgenograms are utilized, seem to outweigh the advantages as a case finding method in tuberculosis.

In view of all of the above considerations, it seems reasonable to rely on general hospital precautions to decrease the exposure of the nurses and hospital workers to tuberculous infection. These include strict isolation techniques for known active cases and the use of routine chest x-ray films for patients admitted to the hospital.

Since a large proportion of the student nurses are initially tuberculin negative on admission to nurses training, tuberculin skin testing may be done frequently to detect infection in this group. If frequent skin tests are to be substituted for frequent chest x-ray films as a method for early case finding of tuberculosis, BCG immunization must not be attempted.

Those who present initially with tuberculin positive reactions may be examined with full size chest x-ray films rather than the photoroentgenograms, and this should be done at less frequent intervals than heretofore in order to avoid excessive radiation exposure.

SUMMARY AND CONCLUSIONS

1. Seventy per cent of our student nurses were tuberculin negative on admission to nurses training.

2. One BCG vaccination "sensitized" 73 per cent of the tuberculin negative student nurses.

3. Thirty per cent of the sensitized students were found to have reverted to tuberculin negative status after two years.

4. With a program of BCG administration frequent chest x-ray films are needed in order to find early tuberculous lesions. Excessive radiation may result especially if photoroentgenograms are used for this purpose.

5. We feel that under present conditions, student nurses who are in good health, with good living conditions can be safely managed through a training period of general nursing and tuberculosis nursing with a minimum of danger. Rather than vaccination, measures utilizing early case finding techniques such as frequent skin testing plus regular chest x-ray films when indicated, are needed. Detection and eradication of previously unsuspected sources of infection, early and adequate treatment of tuberculosis when discovered, and isolation of individuals in the communicable phase of their disease are still our most important means for the prevention of tuberculosis.

RESUMEN

1. Setenta por ciento de nuestras estudiantes de enfermería eran tuberculino negativas al ser admitidas para su adiestramiento.

2. Después de vacunación con BCG entre las tuberculino negativas, 73 por ciento se sensibilizaron.

3. Trienta por ciento de las estudiantes que se sensibilizaron, se encontró que retroviraron a la negatividad después de dos años.

4. Con un plan en que se use BCG se necesitan frecuentes radiografías de tórax para descubrir tempranamente la tuberculosis. Puede resultar una excesiva radiación especialmente si se hacen fotofluorograf'as para ese objeto.

5. Creemos que en las condiciones actuales, las estudiantes de enfermería, en buenas condiciones ambientales pueden observarse a través del período de adiestramiento de enfermería general y de tuberculosis con un mínimo de peligro.

Más bien que inmunización pueden emplearse medidas para encontrar los casos por las reacciones cutáneas más las películas corrientes de rayos X de tórax, cuando se necesiten.

La detección y la erradicación de fuentes antes insospechadas de infección, el cuidado temprano y el adecuado tratamiento de la tuberculosis cuando se descubra y el aislamiento de las personas encontradas en la etapa comunicable, constituye aún nuestros medios más importantes de prevención de esa enfermedad.

RESUMÉ

1. 70% des élèves infirmières de l'auteur avaient des réactions tuberculiniques négatives lors de l'admission aux cours.

2. Une seule vaccination par le B.C.G. fit virer les réactions de 73% des étudiantes porteuses de réactions négatives.

3. 30% des élèves leurs réactions sous l'influence du B.C.G. négativèrent à nouveau leurs réactions au bout de deux ans.

4. Avec un programme de vaccination par le B.C.G. on a besoin de radiographies thoraciques fréquentes pour découvrir les lésions tuberculeuses précoces. Il peut en résulter une radiation excessive surtout si des radiophotographies sont utilisées dans ce dessein.

5. Nous pensons que dans les conditions actuelles, les élèves infirmères qui sont en bonne santé, qui vivent dans de bonnes conditions, peuvent être amenées sans danger à poursuivre une période d'apprentissage concernant la médecine générale et la tuberculose, avec un minimum de danger. Plutôt que l'immunisation, il est nécessaire d'avoir recours aux techniques de dépistage précoce, telles que les tests cutanés associés au film thoracique régulier quand il est indiqué. La détection et l'éradication des sources d'infection antérieurement insoupçonnées, le traitement précoce et convenable de la tuberculose quand elle est découverte et l'isolement des individus pendant la phase contagieuse de leur affection sont encore nos moyens les plus importants pour la prévention de la tuberculose.

ZUSAMMENFASSUNG

1. 70% unserer Lernschwestern waren "Tuberkulin-negativ" zu Beginn der pflegerischen Ausbildung.

2. Eine BCG-Impfung sensibilisierte 73% der "Tuberkulin-negativen" Lernschwestern.

3. 30% der sensibilisierten Schülerinnen waren nach 2 Jahren wieder zu "Tuberkulin-negativem" Verhalten zurückgekehrt.

4. Für ein programm des BCG-Einsatzes sind Thoraxröntgenfilme ständig erforderlich, um tuberkulöse Früherkrankungen zu finden. Es kann sich eine überstarke Strahlenbelastung ergeben, besonders wenn Schirmbilder zu diesem Zweck eingesetzt werden.

5. Wir sind der Überzeugung, daß unter den gegenwärtigen Bedingungen Lernschwestern, die einen guten Gesundheitszustand aufweisen und mit guten Lebensbedingungen, durch eine Ausbildungszeit der allgemeinen under der tuberkulösen Pflege mit einem Minimum an Gefahr sicher geführt werden können. Eher als eine Immunisierung sind solche Maßnahmen erforderlich, die Gebrauch machen von der Technik der Suche nach Frühfällen wie z.B. häufige Hautproben zusammen mit regelmässigen Thorax-Röntgenaufnahmen, wenn diese indiziert sind. Auffindung und Beseitigung von zuvor unverdächtigen Infektionsquellen, frühzeitige und zweckmässige Behandlung der gefundenen Tuberkulösen und Isolierung der Kranken während ihrer infektiösen Phase stellen noch immer unsere wichtigsten Mittel dar zur Verhütung der Tuberkulose.

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Bronchial Catheter Guide for Introduction of a Bronchial Catheter

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The recent advances in pneumonology and thoracic surgery increase the need for detailed investigations of the respiratory tract. Bronchial catheterization is frequently required for bronchography, bronchial aspiration and endobronchial medication. In bronchography, uniformally good results are obtained by using a bronchial catheter, and selective lobar or segmental bronchograms may be taken. Endobronchial medication by bronchial catheter is favoured by some.

From time to time, various techniques have been employed for smooth and satisfactory insertion of a bronchial catheter. Even in highly skilled hands, with adequate local anaesthetic, direct insertion of a catheter excites the cough reflex, which dislodges the catheter in some cases. Insertion of a bronchial catheter by bronchoscope or laryngoscope needs skill and is only possible in specialized units. Another method, recommended by Jackson and Bonnier, is the introduction of a rubber catheter on a soft wire flexible stylet guided by a laryngeal mirror. This requires considerable skill and practical experience.

An instrument called the "bronchial catheter guide" has been designed to overcome the drawbacks of the various methods practiced so far, with an additional advantage that no special training or skill is necessary. In post-operative atelectasis, acutely ill patients need not be submitted to bronchoscopic aspiration in an operation theatre, as aspiration can be done with the help of this instrument at the bed side.

The Bronchial Catheter Guide is manufactured and supplied by Medicon, EGMBH, Tüttlingen, West Germany.

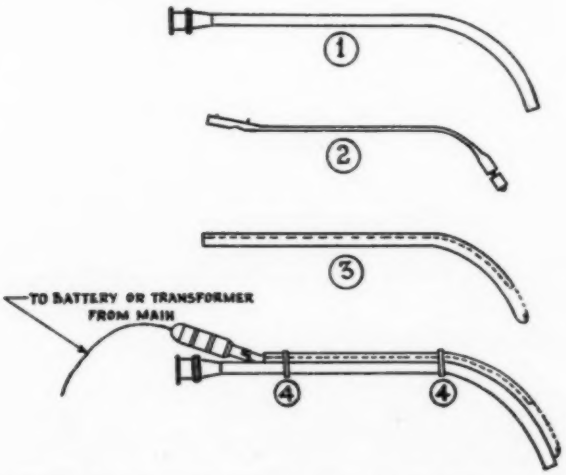

FIGURE 1: Bronchial catheter guide and its components.

The "bronchial catheter guide" consists of the following parts:

1. A hollow stainless steel, chromium plated tube 10.5″ long curved at right angles at its distal end.
2. A stainless steel bulb holder, with bulb.
3. A plexiglass illuminator with concave undersurface, to fit over the bulb holder and the bulb and rest tightly on tube No. 1.
4. The three components are held in position by two stainless steel grips.

Method of Introduction

After thorough anaesthetization of the pharynx and larynx with ½ per cent pontocaine spray followed by cocainization with 5 cc. of 10 per cent solution, the patient's tongue is held firmly as far forward as possible. The operator, after depressing the tongue with a tongue depressor, introduces the catheter guide, loaded, with catheter visible at the distal end, till the posterior surface of the epiglottis is reached. An assistant then pushes the catheter to a sufficient length. The instrument is slowly withdrawn up to the posterior surface of the tongue, then the catheter is held in its place by laryngeal forceps and the guide with-

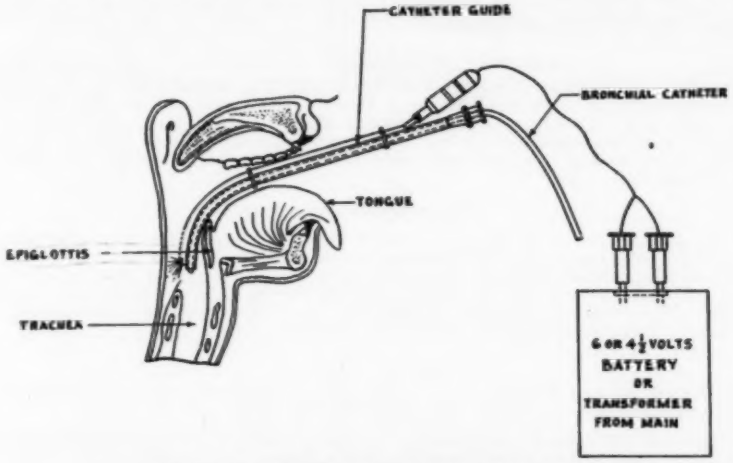

FIGURE 2: Bronchial catheter guide in situ.

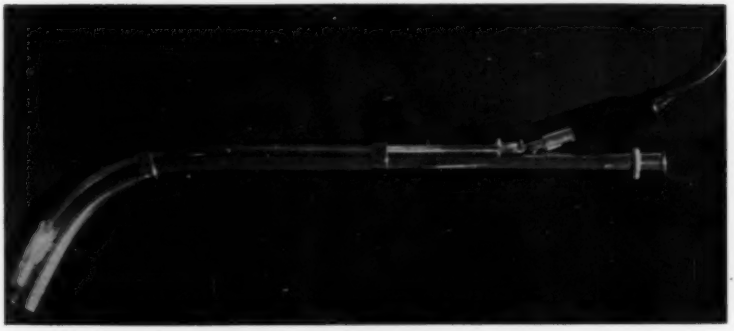

FIGURE 3: Bronchial catheter guide.

drawn. The catheter can be manipulated into the required position under a fluoroscopic screen if desired, for example in bronchography.

Comment

The purpose of this paper is to illustrate an easy method of introducing a bronchial catheter for the average doctor. By using the "bronchial catheter guide," catheterization can be done without difficulty and so should encourage more hospitals and clinics to do bronchograms, bronchial aspiration and endobronchial medication, where previously it was not done.

ACKNOWLEDGMENT: Thanks to Messrs. Willy Rüsch, Rommels Hausen, West Germany, for supplying metras bronchial catheters.

SUMMARY

A "bronchial catheter guide" has been designed to pass the bronchial catheter easily into the trachea through the larynx. This consists of a hollow stainless steel tube with a plexiglass illuminator. After anaesthetizing the throat, it is put on the posterior surface of the epiglottis and the bronchial catheter is pushed in. The guide is withdrawn when sufficient length of catheter has been introduced.

RESUMEN

Se ha ideado un "conductor para cateter bronquial" que permite pasar el cateter bronquial facilmente dentro de la tráquea a través de la laringe.

Consiste en un tubo hueco de acerco inoxidable con un iluminador de plexiglass. Después de anestesiar la garganta se coloca en la superficie posterior de la epiglotis y el cateter bronquial es empujado hacia adentro. Se retira el conductor cuando ha entrado suficiente largo del cateter.

RESUMÉ

Un "guide de cathéter bronchique" a été conçu pour passer aisément le cathéter bronchique dans la trachée à travers le larynx. Il consiste en un tube métallique inoxydable creux avec un système lumineux en plexiglass. Après anesthésie de la gorge, il est mis en place à la surface postérieure de l'epiglotte et le cathéter bronchique est poussé dedans. Le guide est retiré lorsqu'une longueur suffisante de cathéter a été introduite.

ZUSAMMENFASSUNG

Es wurde ein "Bronchus-Katheter Führer" entwickelt, um den Bronchialkatheter leicht durch den Larynx in die Trachea einzuführen. Er besteht aus einem hohlen, rostfreien Stahltubus mit einer Beleuchtungseinrichtung aus Plexiglas. Nach Anästhesie des Rachens wird auf die rückwärtige Fläche des Kehldeckels das Gerät gelegt und der Bronchialkatheter darin eingeleitet. Das Führungsgerät wird entfernt, so bald ein genügend langes Katheterende hindurchgeführt ist.

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A Scapular Attachment for the Finochietto Rib Spreader

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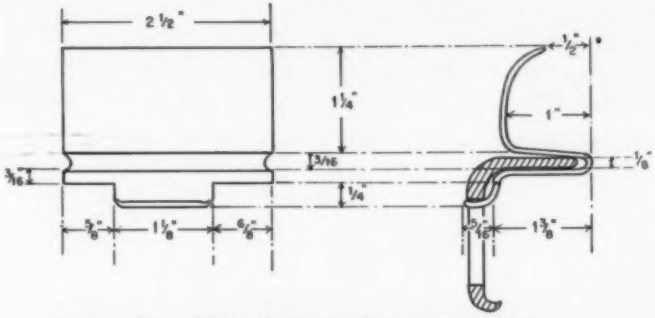
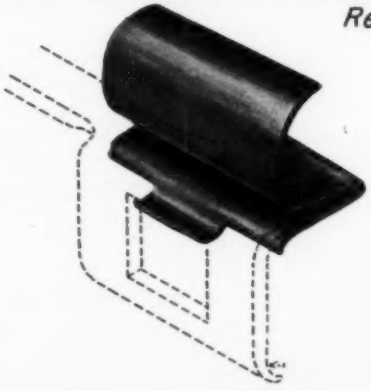
The Finochietto self-retaining retractor[1] is one of the most serviceable of the various rib spreaders designed for intrathoracic surgery. It is at present widely used throughout the world, and, since the instrument is virtually indestructible, most institutions have old models. These are not equipped with a detachable blade (such as that suggested by Harken**) for holding the scapula. This lack of a scapular attachment limits the usefulness of these Finochietto retractors which would be otherwise satisfactory for many further years.

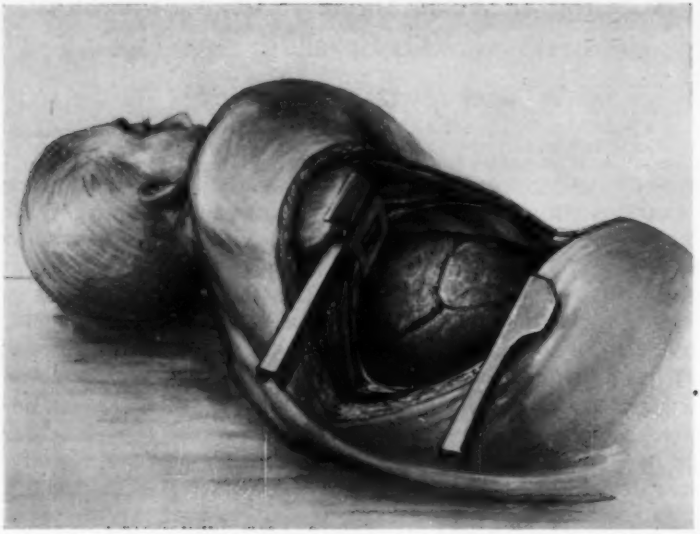
In Figures 1 and 2 are illustrated a scapular blade which can be easily made locally and which requires no modification of the Finochietto retractor itself. The device is simply clipped onto the rib spreader whenever it is desired to hold the angle of the scapula out of the field in high posterolateral thoracotomy incisions. If made of such a material as 3/16 inch stainless steel sheeting and then dull-finished, the scapular attach-

*Surgical Service, U.S.V.A. Hospital, San Francisco, California.
**Manufactured by Codman and Shurtleff, Inc., Boston, Mass.



Scapular Attachment for Finochietto Retractor





ment is sturdy, light and non-reflecting. The curved hollow of the blade supports the angle of the scapula securely yet unobstrusively since it stands out a minimum distance from the chest wall.

It may be that a similar attachment has already been described, but no reference to it could be found. Experience with the local fabrication and use of this type of scapular blade in a number of different hospitals over the past five years has shown it to be inexpensive and practical.

ACKNOWLEDGMENT: The technical assistance of Mr. William Bragg, Nursing Aide, U.S.V.A. Hospital, San Francisco, is gratefully acknowledged.

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SECTION ON CARDIOVASCULAR DISEASES

Further Observations on Hydrochlorothiazide in the Treatment of Congestive Heart Failure

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Chlorothiazide, the first member of the benzothiadiazine family to become available for use, achieved almost immediate clinical popularity as an effective oral diuretic. More recently, another thiazide derivative, hydrochlorothiazide, has been introduced. The initial clinical reports[1-3,5,6] have suggested that the newer drug possesses distinct pharmacologic advantages over chlorothiazide in regard to its greater diuretic effectiveness and lesser kaliuretic response. It is the purpose of this report to review our experiences with a large series of patients with congestive heart failure treated with hydrochlorothiazide.*

Material and Methods of Study

Fifty consecutive hospitalized patients were treated for congestive heart failure with hydrochlorothiazide. Subjects with rheumatic, arteriosclerotic, and congenital heart disease were included.

Thirty-two (64 per cent) of the patients had been on a previous diuretic regimen without successful control of the congestive failure. It is of particular interest that 26 of these individuals had previously received chlorothiazide in varying but adequate doses. The remaining 18 (36 per cent) had not received prior diuretic therapy.

All patients were placed on a 1 gram low salt diet and kept at bed or chair rest while in the congestive state. In addition, each subject was digitalized. No one was started on hydrochlorothiazide until his weight had stabilized on this initial regimen. Thus, each patient served as his own control.

The daily dosage of hydrochlorothiazide varied from 50 mg. (five patients) to 400 mg. (nine patients). Three subjects received 100 mg. per 24-hour period. Eighteen patients were given 150 mg. daily, and 15 others received 300 mg. per day (See Table 1). In no instance were prophylactic electrolyte supplements given.

The following baseline studies were obtained: serum electrolytes (sodium, potassium, chlorides and CO_2), complete blood count, urinalysis, and blood urea nitrogen. Thereafter, these studies were repeated at weekly intervals.

Findings

Complete control of congestive failure was achieved in 43 (86 per cent) of the 50 subjects. An incomplete diuretic response was obtained in four

*Supplied as Esidrix from the Clinical Investigation Division, Ciba Pharmaceutical Products, Inc., Summit, New Jersey.

TABLE 1

SUMMARY OF 50 PATIENTS TREATED WITH HYDROCHLOROTHIAZIDE

						TOTALS
Daily dosages (mg.)	50	100	150	300	400	—
Number of patients	5	3	18	15	9	50
No previous diuretics	3	2	2	7	4	18
Unresponsive to previous diuretic regimen	2	1	16	8	5	32
Control of failure with hydrochlorothiazide						
Complete	5	3	12	15	8	43
Incomplete	—	—	4	—	—	4
Failure	—	—	2	—	1	3
Average weight loss with hydrochlorothiazide (lbs.)	9.4	10.3	10.6	8.8	12.7	10.3 (Average)
Days required	6.2	5.3	6.7	4.3	5.0	5.5 (Average)
Untoward reactions						
Nausea	—	1	2	2	2	7
Skin rash	1	—	—	—	—	1
Digitalis toxicity	—	—	—	—	1	1
Hypokalemia	—	—	—	—	2	2

others (8 per cent). However, in three patients (6 per cent), hydrochlorothiazide failed to produce any diuresis at all.

Twenty-six of the 32 patients who had failed to respond to a previous diuretic regimen were controlled with the use of hydrochlorothiazide. Of particular interest is the fact that hydrochlorothiazide successfully controlled congestive heart failure in 24 instances in which chlorothiazide had previously failed.

The average total weight loss achieved with the various dosages of hydrochlorothiazide ranged from 8.8 to 12.7 pounds. The time required for control of the congestive state varied from 4.3 to 6.7 days; and the most rapid response was attained with the 300 mg. daily dosage (See Table 1).

The incidence of side effects was low. Seven patients (14 per cent) complained of nausea; however, only in one instance was it necessary to discontinue the drug because of this complaint. One developed transient non-pruritic maculoerythematous rash on the extremities and trunk. Digitalis toxicity developed in one subject and profound weakness associated with hypokalemia occurred in two others who were receiving 400 mg. daily. Although a mild to moderate hypochloremic alkalosis occurred in many subjects, this abnormality was not accompanied by signs or symptoms of electrolyte imbalance.

Discussion

Clinical pharmacologic studies have demonstrated that hydrochlorothiazide is a potent diuretic that resembles chlorothiazide qualitatively, but is at least 10 times more active.[2,3] The diuretic potency of hydrochlorothiazide was strikingly demonstrated in the present study in which 43 (86 per cent) of 50 patients with congestive heart failure were completely controlled with the use of the newer drug.

In comparison with the mercurial diuretics, Ford[2] has demonstrated that hydrochlorothiazide is 1.4 times as potent following oral administration as meralluride following parenteral administration. In contrast, it has been demonstrated that chlorothiazide is only 80 per cent as potent orally as parenteral meralluride.[4] In the present study, the increased potency of hydrochlorothiazide appears to be confirmed

by the fact that 24 of 26 patients who had been refractory to chlorothiazide were subsequently completely controlled with hydrochlorothiazide. These findings imply a definite clinical advantage for hydrochlorothiazide.

Both thiazide derivatives have marked natriuretic properties, however, the urinary loss of potassium is significantly less following the administration of the newer drug. The present study confirms this lesser kaliuretic response, as there was no instance of hypokalemia (or digitalis toxicity) except in three patients who had received 400 mg. hydrochlorothiazide daily. These findings indicate an additional clinical advantage for hydrochlorothiazide.

The incidence of side effects was low. Nausea occurred in seven of 50 patients (14 per cent) and a minor skin rash occurred in one subject (2 per cent). Although a mild to moderate hypochloremic alkalosis frequently occurred, this was a reflection of the diuretic effectiveness of the drug rather than a complication. There was no apparent explanation for the lack of diuresis in the three patients who failed to show any response to hydrochlorothiazide.

In view of the rapidity of response obtained with doses of 300 mg. daily, without any accompanying increase in toxicity or hypokalemia, it is recommended that severe heart failure be treated with 200 to 300 mg. hydrochlorothiazide daily. After cardiac compensation has been achieved, a maintenance dose of 25 to 100 mg. per day will usually be satisfactory.

SUMMARY

Forty-three (86 per cent) of 50 patients with congestive heart failure, 32 of whom had been refractory to previous diuretic therapy, were completely controlled with hydrochlorothiazide. The latter drug was effective in 24 instances in which chlorothiazide had failed. The incidence of side effects was low and significant electrolyte disturbances did not occur in dosages below 400 mg. daily.

A dosage of 200 to 300 mg. hydrochlorothiazide daily is recommended for the treatment of severe heart failure. Thereafter, a dose of 25 to 100 mg. per day will usually maintain the compensated state.

The use of hydrochlorothiazide represents a significant advance in the therapeutic armamentarium for congestive heart failure.

RESUMEN

De 50 enfermos con insuficiencia congestiva del corazón, se controlaron con hidroclorotiazida cuarenta y tres (86 por ciento), siendo 32 de ellos, refractarios al tratamiento diurético previo.

La droga mencionada fué efectiva en 24 casos en que la clorotiazida había fracasado.

La frecuencia de efectos colaterales fué baja y no ocurrieron trastornos electrolíticos significantes a las dosis debajo de 400 mg. diarios.

La dosificación de 200 a 300 mg. de hidroclorotiazida diaria, se recomienda para el tratamiento de la insuficiencia cardiaca grave. Más tarde, la dosis de 25 a 100 mg. por día mantendrá el estado de compensación.

El uso de la hidroclorotiazida, representa un avance de significación en el armamentario terapéutico de la insuficiencia cardiaca congestiva.

RESUMÉ

Sur 50 malades atteints d'insuffisance cardiaque, dont 32 avaient été réfractaires à un traitement diurétique antérieur, 86% furent complètement rétablis par l'hydrochlorothiazide. Ce produit fut efficace dans 24 cas où la chlorothiazide avait échoué. La toxicité s'est montrée faible, si bien qu'il n'y eut pas de perturbations électrolytiques nettes pour les doses inférieures à 400 mmg. par jour.

Une dose quotidienne de 200 à 300 mmg. d'hydrochlorothiazide est recommandée pour le traitement des atteintes cardiaques graves. Ensuite une dose de 25 à 100 mmg. par jour permettra généralement de maintenir la compensation.

L'utilisation d'hydrochlorothiazide représente un progrès net dans l'armement thérapeutique de l'insuffisance cardiaque.

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Modification of Lung Compliance During Perfusion with Pump-Oxygenator (Experimental)*

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Introduction

Mechanical factors of lung ventilation have been studied under various conditions since the works of Rohrer,[1] Wirtz and Neergaard.[2] Clinical application was reached with the well-known papers of Dean and Visscher[3] and Otis and others.[4]

Because of the resistances aroused by such a displacement, the action of a series of forces or pressures is required for moving a volume of a gas to or from the pulmonary alveoli. Elasticity, air flow and viscous resistances should be recalled among those which are opposed to the movement of said gas or ventilating air. The magnitude of these complex components has been made accurately measurable by the development of new technical devices and methods.

Pressure necessary for the movement of an air volume to or from the pulmonary alveoli is always equal to the algebraic addition of the pressures necessary to overcome the aforementioned resistances. Thus, as already done by Fry and others,[5] if we assume Pt to be the total pressure necessary for the overcoming of all the resistances, and accordingly, Pe, the pressure necessary for overcoming the elastic resistance, Pv for the displacement or deformation of the tissues when the volume of the lung is augmented or diminished, and Pf the resistance caused by the displacement of air in the pulmonary airway, we can state:

$$Pt = Pe + Pv + Pf$$

The sign of each of the adding figures depends on the breathing phase in which measurement is done, and of course, on the total pressure too. If by means of a special device or by using the technical method, we succeed in measuring the pressure while no air movement is produced, Pf and Pv will be zero and thus:

$$Pt = Pe$$

That is to say, the total pressure (measured in the trachea, pleural space or esophagus), will be equal to that which is necessary for overcoming the elastic resistance.

In this work, our aim was to analyze the elastic behavior of the dog's lung, while circulation was excluded "in vivo," using an extra-corporeal circulating pump for the corresponding by-pass.[6]

Method

Eleven mongrel dogs were used, their weight varying between 8.3 and 20 kg. Pre-anesthetic, anesthetic and surgical methods, as well as the apparatus that were employed, have already been referred to in previous

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papers.[7,8] The endotracheal tube of the anesthetized dog in complete apnoea, with both pleural spaces widely opened through large thoracotomy, is connected to an apparatus consisting of two large glass reservoirs, each calibrated for 50 cc. to 500 cc. One of them is filled with water and the other with oxygen. They are connected at the bottom. The connection to the endotracheal tube ends in a Y shaped tube, a branch of which is connected to a water manometer, and the other to the top of the oxygen reservoir. The communication between the two flasks is opened and 100 cc. of water are allowed to enter the oxygen reservoir. The same volume of oxygen is forced to enter the dog's lung. Then the tracheal pressure is read on the water manometer. This is repeated until a total of 500 cc. of gas enters the lung and the corresponding pressures are recorded. More than one reading was done for each of the stages in almost every case and the average taken. Results were plotted in a Pressure-Volume diagram such as shown in Fig. 1. It belongs to dog No. 39 and the remaining data can be found in the same Figure. All the diagrams were obtained on inspiration. Point of volume zero represents the point of maximum spontaneous retraction of the lung. Before each reading, the lungs of the recipient were amply and repeatedly insufflated in order to eliminate the atelectatic zone which might be produced.

Calculations

The curves being lineal, the coefficients were easily found. The elastic coefficient of the lung can be expressed by the following equation:

$$K = \frac{dP}{dV}$$

That is to say, the rate of increment of pressure referred to the incre-

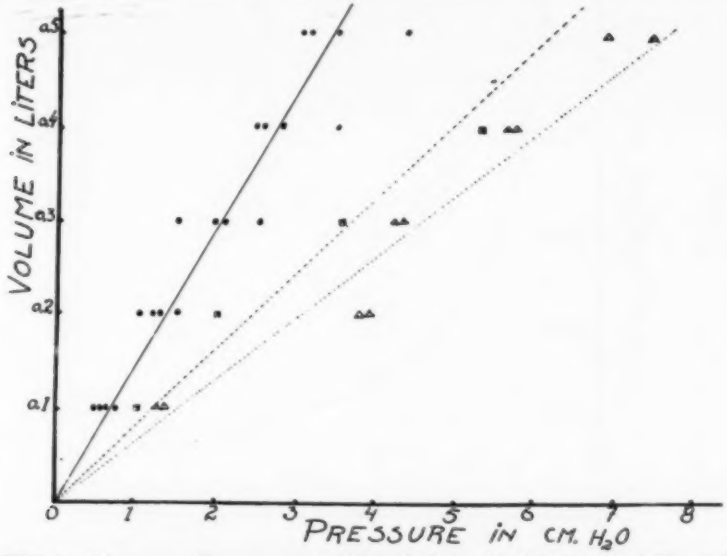

FIGURE 1: Lung compliance curves obtained from dog N° 39, of 16 Kg. weight, being perfused for 13 minutes. ● = Before perfusion, △ = During perfusion, □ = After perfusion.

TABLE 1

DOG No.	WEIGHT KG.	COMPLIANCE COEFFICIENT L/cm.H_2O			ELASTANCE COEFFICIENT cm.H_2O/L			PERFUSION TIME Minutes
		Before	During	After	Before	During	After	
32	20	0.142	0.083	0.166	7.00	12.00	6.00	25
			0.073					
33	10.5	0.078	0.052	0.058	12.4	19.00	17.00	48
			0.050					
34	8.3	0.071	0.040	0.052	14.00	25.00	19.00	30
34 bis	19	0.151	—	—	—	—	—	—
35	15.5	0.241	0.100	0.138	4.40	10.44	7.2	42
			0.090					
36	12.5	0.069	0.062	0.080	14.40	16.00	12.40	24
37	20	0.166	0.088	0.111	6.00	11.20	9.00	29
38	19.5	0.182	0.090	0.131	5.3	11.00	7.60	24
			0.090					
39	16	0.151	0.071	0.075	6.6	13.8	12.2	13
			0.067					
40	15.5	0.070	0.058	0.053	14.00	17.00	19.00	15
41	18.5	0.154	0.100	0.125	6.46	10.00	8.00	50
			0.090					
Average	15.8	0.134	0.075	0.098	8.81	14.64	12.08	30

ment of volume (expressed in cm. H_2O/liter). It depends on the elastic nature of the body or system under consideration. This almost exclusive dependence is governed by the static conditions of the experiment, with neither air nor flow nor tissue deformation caused by movement.

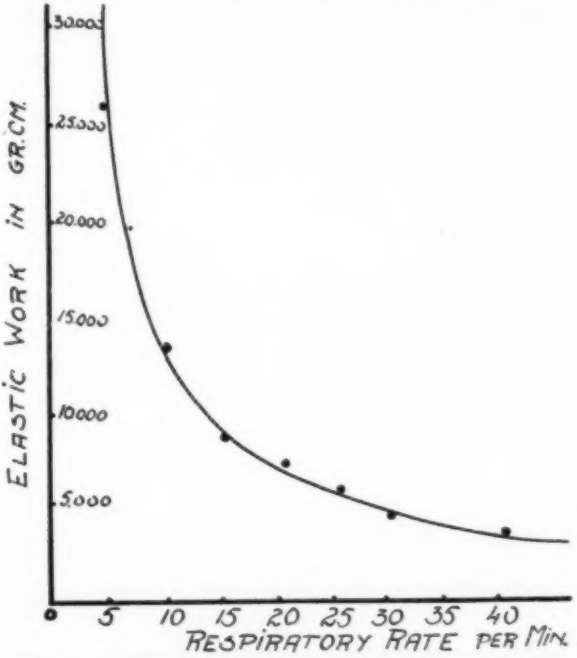

FIGURE 2: Relation between elastic work and respiratory rate. Each point corresponds to the values given in Table 4. (Dog N° 36).

TABLE 2

DOG No.	ELASTIC WORK (gm. cm.)		
	Before	During	After
32	875	1,500	750
		1,700	
33	1,500	2,375	2,125
		2,500	
34	1,750	3,050*	2,375
34 bis	825		
35	525	1,250	900
		1,300	
36	1,800	2,000	1,550
37	750	1,400	1,125
38	1,250	2,750	1,900
Average	1,159	1,982	1,503

*Volume introduced was only 400 cc. and the corresponding work 2,000 gm. cm. Extrapolation for 500 cc. gives 3,050 gm. cm.

Lung compliance is expressed by the inverse of the elastic coefficient, and can be defined by the volume that can be moved to or from the alveolus with a pressure gradient of 1 cm. H_2O.

Work elastically accumulated during the inhalation of 500 cc. of gas beginning at the level of complete spontaneous collapse, was also calculated. A simplified equation,[9] corresponding to the area of the triangle formed by the P-V curve and the pressure axis, was used:

$EW = 0.5\ P \cdot V$ were EW: elastic work in gm. cm.

P: pressure in gm./cm.^{2}

V: Volume in cm.^{3}

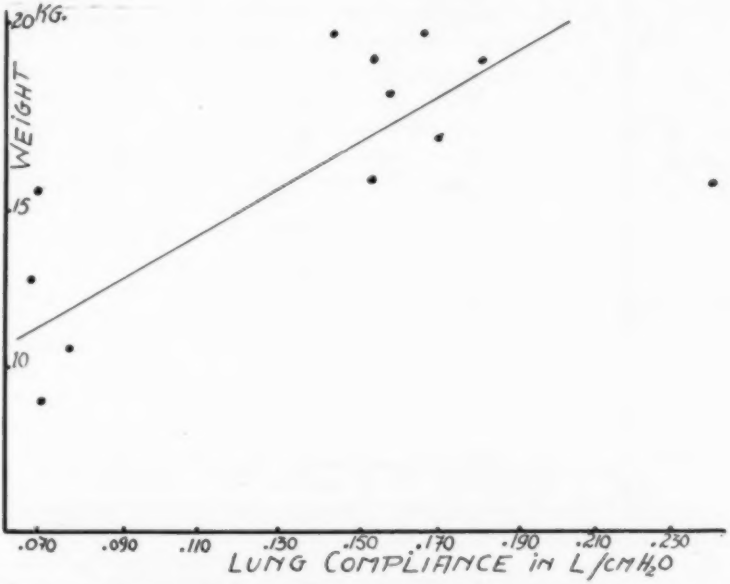

FIGURE 3: Relation between Compliance and dogs weight (see text).

TABLE 3 — ELASTIC WORK AT FREQUENCIES VARYING BETWEEN ZERO AND 40 BREATHING PER MINUTE, AND A MINUTE VOLUME OF 4,000 cc. (DOG No. 36)

Respiratory Rate (per minute)	Elastic Work (gm. cm.)
40	3,200
35	3,430
30	4,230
25	5,300
20	6,400
15	8,475
10	12,800
5	25,600

Dean and Visscher[3] have shown in dog lungs that a second is enough for the setting of equilibrium of pressures upon the introduction of 100 cc. of a gas, and therefore after that period, pressure will only depend on the elastic capacity of said lung, with no viscous resistance effect. In such conditions, the indicated area only measures the elastic work.

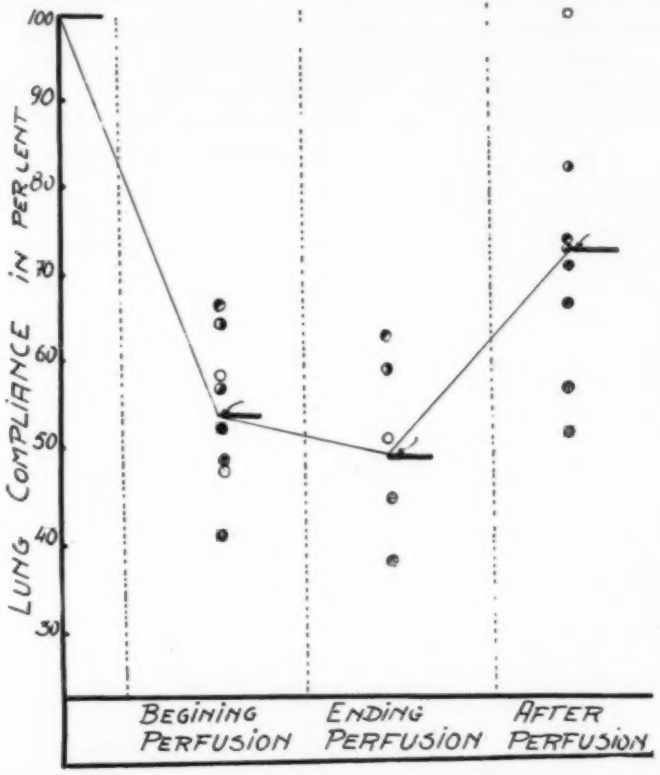

FIGURE 4: Modification of lung distensibility during and after perfusion, in relation with the values obtained before perfusion, expressed as per cent of it. The arrows correspond to average values.

Results

1. *Lung compliance:* As shown in Table 1, the compliance coefficient varied between 0.069 and 0.241 L/cm. H_2O before the perfusion was started. The average was 0.134 L/cm. H_2O. Distensibility clearly diminished while the pump was operating. Minimum was 0.040 and maximum 0.100 L/cm. H_2O (average 0.075). In some dogs (No. 32, 33, 34, 38, 39, 41), coefficients were calculated before finishing the perfusion, and decrease in compliance was seen to be more accentuated. After the end of perfusion and upon the return of lung circulation, lung distensibility shows improvement in some cases, and in others a tendency to recover values obtained before the perfusion was started. The lowest coefficient was 0.052 and the highest 0.166 L/cm. H_2O, (average 0.098). Dog No. 36 showed a broncho-pleural fistula, probably of traumatic origin, and therefore the corresponding figures should not be considered as absolute. As it can be noticed, compliance coefficient was higher at the end of perfusion than at the beginning, because the fistula provided for an escape of pressure during the measurements. After localizing and suturing it, the coefficient was 0.080 L/cm. H_2O.

2. *Elastance Coefficient:* Its characteristics are similar to those of the compliance coefficient. The smallest value was 4.20 and the highest 14.4 cm. H_2O/L, with an average of 8.81 cm. H_2O/L before the total by-pass. During it, a marked increase of the coefficient was noticed. Minimum being 10.4, maximum 25 and average 14.64 cm. H_2O/L. A trend to an increase of the coefficient was recorded as the experience was lengthened (dogs No. 32, 34, 35, 39 and 41). When perfusion was over, they recovered, and figures of the coefficient were 6.00, 19.00 and 12.05 cm. H_2O/L as the smallest, highest and average values. As to dog No. 36, remarks made when considering compliance are also valid here.

3. *Work accumulated against elastic resistance:* Table 2 shows the results obtained for dog No. 38. The first column shows the values calculated before perfusion (525, 1,800 and 1,159 gm. cm. as minimum, maximum and average). The second column shows figures during perfusion with a minimum of 1,250, maximum 3,050, and average of 1,982 gm. cm. As shown in the third column, there is a decrease of the work required in order to overcome the elastance corresponding to the introduction of 500 cc. of gas, if the perfusion period is itself compared with the post perfusion period: 750, 2,300, and 1,503 gm. cm. as minimum, maximum and average values. These figures illustrate the increase of the resistance to breathing during and after the perfusion proceeding. They are minute volumes, but we wanted to find the dynamic resultant in order to state the relation between elastance and breathing frequence as found by other authors. Thus assuming a minute volume of 4,000 cc. per minute, (without considering, for sake of simplicity, the dead space) calculation of elastic work has been made for dog No. 36 with frequencies ranging from 0 to 40 breaths per minute (Table 3). The corresponding diagram was drawn and we noticed (Fig. 2) that the curve becomes asymptote to the frequencies axis (the curve being an equilateral hyperbola). This curve corresponds to that obtained by other authors,[19] and means that the

elastic work decreases with breathing frequence. This is a logical conclusion because of its inverse relation with the tidal volume at a certain minute volume.

Discussion

Various interesting considerations arise from the stated data. Some of them confirm other authors' results in the field of ventilatory mechanics.

1. *Lung compliance:* Upon considering the figures obtained with our method, the apparent disparity of the available data is noticed, but actually this disparity is not real. If a curve is drawn (Fig. 3) in a Compliance-Weight diagram, the clear relation between both sets of data becomes evident. In other words, compliance depends on the quantity of lung parenchyma in consideration, but the observation of how compliance is modified during the complete by-pass with the pump-oxygenator seems to us the most important single feature of this paper. This is shown in Fig. 4 in which percentages of distensibility modifications are plotted against the surgical process. Surgical maneuvers, atelectasis, bronchial obstructions, are discarded as the only probable causes for this phenomenon, by the fact that the modification tends to disappear or to decrease to a great extent, after the by-pass is finished. Moreover, the practice of wholy distending the lung before the determination eliminates the possibility of the two last contingencies as the exclusive cause. Therefore, the only element left for consideration is the vascular factor which we believe to be the ruling one in this modification of the lung parenchyma.

Decrease in pulmonary compliance of patients with cardiac insufficiency, in mitral stenosis, and other pulmonary congestive diseases has already been described. Acute congestion of the pulmonary vascular bed also causes a fall in the pulmonary compliance. Recently, Bondurant and Hickman[11] proved this for healthy men.

During the by-pass with the pump-oxygenator, we believe that three important factors are related to the modifications of the elastic behavior of the lungs:

a) Vascular stasis caused by interrupting circulation through the lesser circuit. As all local ventilation is accordingly eliminated, stasis may also produce a local tissue anoxia, subsequently modifying the blood vessels diameter, and therefore the anatomic conditions of the lung.

b) Vascular engorgement by injection in the pulmonary vascular bed of the volume of blood coming from the coronary sinus and Thebesian veins, in case of working without induced cardiac arrest and right ventriculotomy. When operating with cardioplegia, this engorgement is produced by the blood that empties the right ventricle before cardiac arrest, and corresponds to the blood that was previously filling it. This happens if the coronary circulation is interrupted by clamping only the aorta.

c) Blood regurgitation through the bronchial system. The close connection between bronchial arterial circulation and pulmonary functional circulation has been already stated.[12,13] In physiological conditions, these connecting vessels are closed, but a small gradient of pressure between both systems is enough for their opening and subsequent arterial blood drainage from the aorta, through the bronchial arteries to the pulmonary functional system. This is probably what happens during the total by-pass, when pressure in the aorta is maintained, owing to its perfusion through the carotid or femoral arteries, and lung circulation is almost null. Thus, steady regurgitation of blood to the pulmonary system, closed on both sides, engorges the lung and increases its rigidity producing the modifications in the coefficients that have already been spoken of. Draining the left atrium during by-pass in new experiences, the authors have been able to correct partially the already mentioned modification of the compliance. This is also an explanation for the elastic modifications when the by-pass is prolonged. When it is over, blood recirculation through the pulmonary system gradually balances the quantity of blood retained in the lung. This, together with ventilation, improves the conditions of local anoxia, as well as circulation, activated by the action of lung movement, and causes the lung to recover gradually the properties it had before the perfusion.

2. *Breathing work against elastic resistance:* The interest in its determination lies in the fact that almost all pathological cases (except in those of generalized respiratory obstruction) and also in normals, elastic resistance represents 60 to 80 per cent of the total resistance for introduction of a certain volume of air in the alveolar space. Therefore, work against such resistance which is performed by the respiratory muscles, will be the most important part of the total breathing work.

The increase in elastic work after perfusion is very significant and strongly suggests considerations of special precautions during post operative period of those patients whose ventilation is limited by thoracotomy, pain, bandages, etc. If these facts are not considered, danger of general and pulmonary complications might bring serious troubles in the recovery of these patients.

SUMMARY AND CONCLUSIONS

Increase of pulmonary elastance was observed during the total by-pass with the pump-oxygenator. Considering the cases individually, the decrease in the distensibility is accentuated during perfusion. No relation has been found between the grade

of decrease in the pulmonary compliance and time of perfusion, on comparing the results of the entire group. Probable causes of this phenomenon are:

a) Regurgitation of blood from the bronchial arteries through the connecting vessels.

b) Injection of blood from the right ventricle to the pulmonary vascular bed at the beginning of the by-pass. This blood is not only that which was actually contained in the ventricle, but also that coming through the coronary bed.

c) Vascular stasis and probably structural modification produced by it, and lack of ventilation with subsequently local anoxia.

Decrease of the pulmonary compliance tends to retrogress when the complete by-pass is over and the grade of recovery depends on the time of perfusion interruption.

The data are correlated with important facts for the follow-up of patient operated by this method.

RESUMEN Y CONCLUSIONES

El aumento de la elasticidad pulmonar se observó durante el paso desviado total de la sangre con la bomba-oxigenadora. Considerando los casos individualmente el aumento de la distensibilidad se acentúa durante la perfusión.

No se encontró relación entre el grado de decrecimiento de la distensibilidad pulmonar y el tiempo de perfusión comparando los resultados de todo el grupo. Las causas probables de este fenómeno son:

a) Regurgitación de sangre de las arterias bronquiales a través de los vasos conectantes.

b) Inyección de sangre del ventrículo derecho al lecho pulmonar vascular al principio de la desviación. Esta sangre no sólo es la que de hecho estaba contenida en el ventrículo sino también la que viene a través del lecho coronario.

c) El éxtasis vascular y probablemente la modificación estructural producida por él y la falta de ventilación con la subsecuente anoxia local.

El decrecimiento de la distensibilidad pulmonar tiende a retrogradar cuando ha terminado la desviación y el grado de recuperación depende del tiempo de la interrupción de la perfusión.

Los datos están en correlación con importantes hechos para la observación de los enfermos operados por este método.

RESUMÉ

L'augmentation de l'élasticité pulmonaire fut observée pendant un court-circuit total par oxygénateur à pompe. En considérant les cas individuellement, la diminution de la possibilité de distension pulmonaire est accentuée pendant la perfusion. On n'a trouvé aucun rapport entre ce degré de diminution et le temps de perfusion en comparant les résultats du groupe entier. Les causes probables de ce phénomène sont:

a) la régurgitation du sang des artères bronchiques à travers les vaisseaux en connection avec elles;

b) l'injection de sang du ventricule droit vers le lit vasculaire pulmonaire au commencement du court-circuit. Ce sang est non seulement celui qui était contenu à ce moment dans le ventricule, mais également celui venant du lit coronarien;

c) la stase vasculaire et probablement la modification de structure produite par elle, et le manque de ventilation avec anoxie locale conséquente.

La diminution de la possibilité de distension pulmonaire tend à régresser quand l'opération complète est terminée et le degré de retour à las normale dépend du temps de l'interruption de la perfusion.

Ces constatations comportent des notions importantes, pour la surveillance des malades opérés par cette méthode.

SCHLUSSFOLGERUNGEN

Eine Eröhung der pulmonalen Elastizität wurde während des vollständigen Nebenschlusses mit dem Pumpen-Oxygenator beobachtet. Betrachtet man die Fälle individuell, wird die Verringerung der Ausdehnbarkeit während der Durchströmung verstärkt. Es fand sich keine Beziehung zwischen dem Grad der pulmonalen Füllung und Durchströmungszeit im Vergleich zu den Ergehnissen der Gesamtgruppe. Mögliche Ursachen dieses Phänomens sind:

a) Rückfluss des Blutes aus den Bronchiolarterien durch die Verbindungsgefäße.

b) Einschliessen von Blut aus dem rechten Ventrikel in die pulmonale Gefäßbahn zu Beginn des Nebenschlusses. Dies ist nicht nur jenes Blut, das sich tatsächlich in der Kammer befand, sondern auch dasjenige, das durch die Coronargefäße fliesst.

c) Vaskuläre Stase und dadurch bewirkte wahrenscheinliche Strukturveränderungen sowie fehlende Ventilation mit nachfolgender lokaler Anoxie.

Die Verringerung der pulmonalen Füllung neigt dazu, sich zurück-zuentwickeln, wenn der vollständige Nebenschluss beendet ist; und das Ausmaß der Erholung hängt ab von der Dauer der Unterbrechung der Durchströmung.

Die Werte werden in Beziehung gesetzt zu wichtigen Faktoren für die Nachbeobachtung von mit dieser Methode operierten Kranken.

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Current Concepts on the Management of Congestive Heart Failure

The term "congestive heart failure" is descriptive of a clinical state which results from inability of the cardiac pump to maintain adequate blood flow to all tissues of the body. Heart failure first becomes evident during periods of increased activity. At such times, the additional demand exceeds the capacity of the heart to increase its load. The clinical manifestations in patients reflect this inadequacy of the pump. A number of secondary hemodynamic and metabolic changes such as sodium retention and edema formation represent imperfect attempts to regain cardiac compensation.

Until recently, seemingly separate clinical entities were explained by the hemodynamic concepts of "forward" and "backward" heart failure. Forward heart failure was considered a clinical state which resulted from a marked reduction in left ventricular output. Its principal manifestations were attributed to decreased perfusion of vital tissues manifested by low arterial pressure, fatigue, and weakness. In the case of the kidney, reduced blood flow presumably led to inadequate excretion of sodium and water with resultant fluid retention and edema formation. Backward failure referred to passive engorgement of the venous system caused by the heart's inability to accept and promptly expel all of the venous blood that was returned to it. Damming up of blood proximal to the failing left ventricle increased hydrostatic pressure in the pulmonary veins and was a major factor in the production of pulmonary edema. Decompensation of the right ventricle resulted in elevation of pressure in the right atrium and in the great veins. Engorgement of veins in the subcutaneous tissues and in the viscera led to augmentation of serous effusions and edema.

Newer Concepts of Pathophysiology

The hydrostatic concepts of "forward" and "backward" failure, though not invalid, have recently been overshadowed by improved understanding of the role of water and electrolyte shifts that occur during cardiac decompensation. Indeed, most of the signs and symptoms of congestive heart failure are in direct consequence of an increase in the quantity and disarrangement in the distribution of body water. Renal clearance studies have shown that sodium retention and accompanying increase in the reabsorption of water are not fully explained by a decrease in blood flow through the kidney. Fluid accumulation is much more closely related to increased reabsorption of sodium and water by the renal tubules in consequence of endocrine factors.

Endocrine Factors

In 1950, powerful sodium retaining substances were detected in the urine of patients with congestive heart failure and edema.[1] These findings, and earlier observations of increased adrenal activity, suggested

that a humoral factor was involved. Three years later, aldosterone, a potent salt retaining hormone of the adrenal gland was isolated. Unusually high plasma and urine concentrations of the hormone were found in patients with congestive heart failure and edema. The postulation that aldosterone was an important humoral factor in sodium retention and edema formation in cardiac patients was promptly confirmed. Clinical studies indicated a close quantitative relationship between increase in aldosterone production and the onset and intensity of congestive heart failure.[3]

The precise mechanism by which the increase in aldosterone production is brought about is as yet obscure. The existence of an arterial receptor which provokes liberation of aldosterone in response to a reduction in arterial blood flow has been proposed.[3] However, retention of sodium was more closely related to a rise of end-diastolic pressure in the right ventricle and independent of cardiac output.[4] In addition, increased excretion of aldosterone followed the experimental production of right heart failure or constriction of the thoracic inferior vena cava in dogs.[5] These data suggest the presence of veno-receptors causing increased secretion of aldosterone in response to elevations in venous pressure.

The activity of the posterior pituitary anti-diuretic hormone (ADH) is increased in the presence of congestive heart failure. This may be an important factor in the case of patients with advanced cardiac failure who are in the final stages of decompensation. In these patients, aldosterone activity is already maximal. ADH activity may be markedly increased in a last ditch effort to maintain blood flow by causing further retention of water with damaging loss of normal osmolarity of the body buids. This mechanism is a minor factor in fluid retention during the initial stages of congestive heart failure.

B. Myocardial Failure

The basic disturbance in congestive heart failure is loss of normal myocardial contractility. This may be the result of mechanical overloading of the muscular pump working against increased resistance (e.g. hypertensive vascular disease, aortic stenosis), mechanical restriction of cardiac contraction (constrictive pericarditis, endocardial fibroelastosis), or the additional burden provided by excessive volumes of blood (e.g. arteriovenous fistula, interatrial septal defect). Myocardial failure may also follow direct injury of cardiac muscle by inflammatory disease (e.g. rheumatic carditis), through the action of toxins (e.g. diphtheritic myocarditis), or following invasion by bacteria or parasites (e.g. trichinosis). If the muscle cells are deprived of adequate blood supply (e.g. coronary atherosclerosis) or essential nutrients (e.g. beriberi heart disease), heart failure is due to a critical lack of essential metabolites.

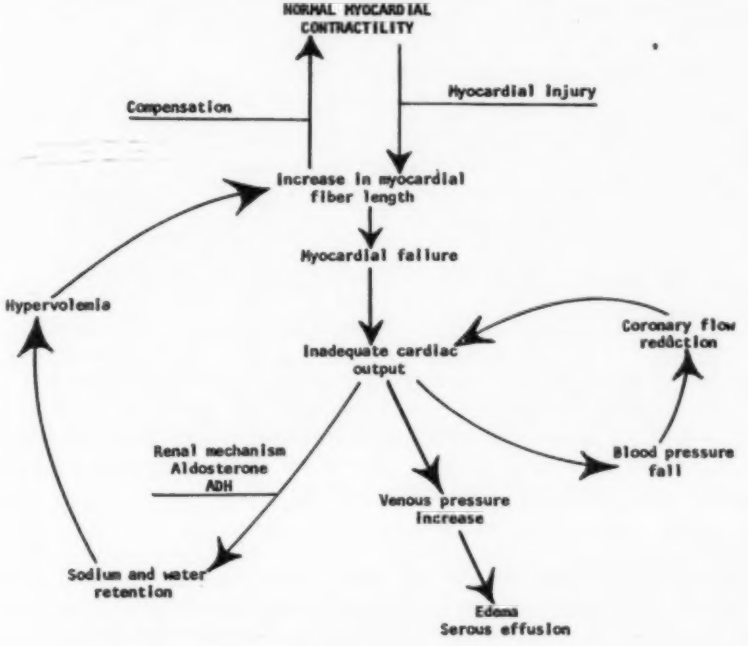
When the heart is unable to expel the quantities of blood that are returned to it, there is compensatory stretching of muscle fibers. Elongation of muscle fibers increases myocardial contractility and therefore the capacity of the heart to do work (Starling). This compensatory change is brought about by augmentation of residual volume of blood in the ventricle at the end of diastole. In effect, myocardial weakness leads to an increase in intravascular volume which then causes disten-

tion of the ventricle. The individual muscle fibers are stretched, contractility is augmented, and systolic work capacity is improved.

Water and Electrolytes

Since an increase in intravascular volume provides a distending force which initially increases myocardial contractility, fluid retention represents a compensatory mechanism. Evidence indicating that these changes are brought about by the aldosterone has already been reviewed. If compensation is not achieved, the aldosterone mechanism is progressively intensified and becomes detrimental. With further retention of sodium and water there is additional enlargement of the heart. Elongation of cardiac muscle beyond an optimal range leads to decreased contractility and further reduction in the work capacity of the heart. This provokes additional aldosterone activity and sodium and fluid retention. Cardiac output falls and blood flow to the coronary system may be critically reduced. Additional myocardial damage may result. In effect, two vicious circles are established (Fig. 1).

With progressive increase in fluid in the interstitial spaces (extravascular space), edema and serous effusions become clinically apparent. Accompanying the increase in the extra-cellular fluid volume is an abnormal ingress of water and sodium into the cells and egress of the potassium that has been displaced by sodium. The potassium is excreted



PATHOPHYSIOLOGICAL RELATIONSHIPS IN CONGESTIVE HEART FAILURE

FIGURE 1

by the kidney at an accelerated rate through a secondary action of aldosterone. These changes impair cell function for the cells now contain abnormal quantities of sodium, decreased potassium, and excessive water. Congestive heart failure thus results not only in a retention of salt and water in the extracellular space, but ultimately in an increase in water in all body compartments and abnormal intracellular concentration of electrolytes.[6] The patient loses his appetite and becomes lethargic and chronically ill in consequence of this generalized cellular disturbance.

Therapeutic Implications

A low salt diet combined with judicious use of diuretics are proven measures in the treatment of heart failure. The practical value of a restricted intake of sodium is unchallenged. However, these measures which are used in an effort to control the electrolyte and fluid disturbance of heart failure may occasionally be too vigorous. Prolonged and excessive use of the diuretic agents has led to secondary derangements that in themselves provide threatening clinical states.

The pendulum has probably swung a little too far in favor of diuretic agents to the exclusion of cardiotonic measures. Since the fundamental disturbance follows a decrease in myocardial contractility, optimal treatment should be directed to restoration of normal myocardial function and secondarily to countering the derangements in fluid and electrolyte retention.

Rest and Sedation

Reduction of the work-load on the heart is a simple, practical and effective therapeutic measure. This is well demonstrated by the prompt diuresis which frequently follows bed rest without any additional treatment. The semi-recumbent position is preferred for it provides a lesser work-load on the heart and favors optimal pulmonary ventilation. If the onset of congestive heart failure is acute, and if fear and resultant anxiety are marked, these are promptly allayed by the use of moderate doses of morphine, 5 to 10 mg (gr 1/6 to 1/12) given hypodermically. Concurrent use of dimenhydrinate (Dramamine sulfate) intramuscularly in a dosage of 50 mg obviates nausea. This may be supplemented or followed by the judicious use of a long acting barbiturate such as butabarbital sodium (Butisol) in doses of 15 to 30 mg (gr ¼ to ½) at intervals of 6 to 12 hours. Inactivity favors venous stasis. Thromboembolic complications in this "high risk" group are reduced by anti-coagulant therapy until cardiac compensation is regained.

Digitalis

Digitalis glycosides remain the most efficacious cardiotonic agents. Their use is followed by improved myocardial contractility, thereby directly countering the primary mechanism of congestive heart failure. In emergency situations, deslanoside (Cedilanid-D) has proven a very satisfactory agent. Digitalization in adult patients is accomplished with a dose of 1.6 mg. Except in patients with hypotension for whom intravenous injection is indicated, the digitalizing dose is given intramuscu-

larly. One-half of this dose may be given initially and the remainder as a divided dose, two and four hours thereafter. In dire circumstances the total digitalizing dose may be given as a single injection intravenously. It is effective within one-half hour. Digoxin (Lanoxin) has the advantage of prompt action, requiring only slightly longer than deslanoside for full effect. Digitalization is accomplished with 1.5-3.0 mg given intramuscularly. Maintenance therapy is accomplished with 0.25 to 0.5 mg daily. In a majority of patients, digitalis leaf remains a very fine preparation if a carefully standardized product is selected. Gastrointestinal warning signs become evident before cardiac toxicity, providing an inherent safety factor. In those patients in whom gastrointestinal symptoms appear on therapeutic dosage of digitalis leaf, a more purified preparation such as digoxin, digitoxin (Crystodigin), acetyldigitoxin (Acylanid), or gitalin (Gitaligin) may be selected. Digoxin and, to a lesser extent, gitalin and acetyldigitoxin are rapidly excreted and therefore reduce the hazard of prolonged over-digitalization.

Recognition that cardiac decompensation may itself be due to digitalis overdosage may be life-saving. Prompt administration of potassium is the treatment of choice. Intravenous administration of a total quantity of 50 meq. in the form of potassium chloride (3.7 gm) diluted in 1000 ml of a 5% glucose solution over a period of three hours is recommended.

Sympathomimetic Drugs

Vasopressor amines such as norepinephrine (Levophed) or metaraminol (Aramine) may offer definitive aid in patients with hypotension accompanying congestive heart failure. These agents have a dual advantage. They improve myocardial contractility by increasing coronary blood flow. In addition, they have a direct action on the myocardium resulting in increased myocardial contractility.[7] In this respect, they supplement the cardiotonic action of digitalis. In critical situations, the sympathomimetic drugs represent a powerful reserve. Metaraminol is particularly advantageous because it can be administered by various parenteral routes. Intravenous injection (1 to 5 mg) at intervals of 15 minutes, continuous intravenous infusion (50 mg per 500 ml of 5% glucose solution), or intramuscular or subcutaneous doses of 5 to 10 mg every one-half to one hour may be employed. Unlike norepinephrine, there is no significant risk of local tissue injury. When used in moderate doses the danger of provoking a major cardiac dysrhythmia with metaraminol or norepinephrine even in the failing heart is very small.

Cardiac Dysrhythmias

Myocardial failure may be related to a disorder of cardiac rhythm. In paroxysmal atrial tachycardia maneuvers to control the dysrhythmia by carotid sinus pressure, the administration of 1 mg of neostigmine (Prostigmin) subcutaneously, or the use of 5 to 10 ml of phenylephrine (Neosynephrine) intravenously should be attempted. If these measures fail or if auricular flutter or fibrillation intervene, rapid digitalization with deslanoside is advised. Instances of supraventricular tachycardia with atrio-ventricular block and ventricular tachycardia may reflect a dangerous level of over-digitalization. Treatment involves the administration of potassium chloride as previously described. Ventricular

tachycardia due to other causes is treated with intravenous administration of procaine amide (Pronestyl) under electrocardiographic control.

Assisted Circulation

The use of an extra-corporeal pump for the maintenance of circulation for brief periods in patients with acute congestive heart failure who would not otherwise survive, has ben proposed and tested. Partial cardiac by-pass has been an effective method for reducing the work-load on the heart.[8] Its clinical application in selected patients has shown promise, but is as yet an experimental technique.[9]

Acute Pulmonary Edema

Pulmonary edema represents an immediate threat to life because of the danger of respiratory anoxia. Oxygen is used initially by mask; subsequently a nasal catheter or tent may be employed. The mask has the advantage of providing a high oxygen concentration. The nasal catheter provides comfort for the patient, while the tent offers the advantage of refrigeration and controlled humidity. Intermittent positive pressure breathing (3 to 6 mm of mercury) and the use of anti-foam agents such as 50 per cent ethyl alcohol or detergents such as superinone (Alevaire) in the humidifier are helpful in reducing frothy edema. The asthmatic component may be markedly lessened by theophylline which must be used with caution if administered intravenously. It may be given rectally by suppository or retention mixture (Clysmathane), or orally, preferrably in an alcoholic vehicle (Elixophyllin).

Removal of Fluid

Pleural effusion or ascites may be a critical factor in the presence of acute pulmonary edema. The presence of fluid in the alveoli impairs diffusion of oxygen into the alveolar capillaries and elimination of carbon dioxide. Pleural effusion and ascites impair alveolar ventilation. The combined effect is intensification of anoxia and respiratory acidosis and this may present an immediate hazard. Prompt employment of thoracic or abdominal paracentesis may be indicated as an emergency procedure.

In dire circumstances, immediate reduction of intravascular volume represents a direct method of reducing the work-load of the heart. Tourniquets may be applied proximally on three extremities to produce a "dry phlebotomy." These are rotated every 20 minutes, leaving blood flow in one extremity unblocked. If the early response to treatment is poor and especially if pulmonary edema is progressive, phlebotomy with immediate removal of 500 to 750 ml of blood is indicated. Under these circumstances, phlebotomy may be life-saving.

Diet

A low-salt diet (200-500 mg sodium per day) has been helpful in the long-term management of fluid retention in the limited group of cardiac patients who adhered to this strict regimen with religious care. With the availability of orally administered saluretic agents, the need for long-term rigid dietary restriction of salt to less than 1.0-2.0 gm daily has been obviated.

Diuretic Drugs

Chlorothiazide (Diuril) in doses of 0.5 mg, one to four times daily, and hydrochlorothiazide (Hydrodiuril, Esidrix) in doses of 250 to 500 mg three times daily, have proven effective and remarkably safe oral diuretic agents except in the presence of liver disease. Unlike the parenterally administered mercurial diuretics where chloride may be lost disproportionately, diuresis from chlorothiazide is associated with balanced excretion of sodium and chloride. The frequency and severity of chlorothiazide and hydrochlorothiazide induced potassium deficiency has probably been overstated. In an occasional edematous patient, vigorous use of diuretic agents may deplete body potassium. In most instances, however, this may be prevented by the intake of citrus fruits and juices or by supplementation with a rather palatable potassium citrate solution (potassium triplex), one teaspoonful three times daily. Hydrochlorothiazide is somewhat easier to swallow because of smaller tablet size, but it has no other definitive advantages over chlorothiazide.

Mercurial diuretics should be reserved for patients in acute congestive heart failure who are in need of parenteral diuretics for a brief period or for patients with liver disease. The principal disadvantage of mercurial diuretics is the preferential excretion of chloride resulting in hypochloremic alkalosis after prolonged use. Intravenous administration is much more hazardous, but not more efficacious than intramuscular use.[10] Meralluride (Mercuhydrin) or mercaptomerin (Thiomerin) may be given in doses of 2cc daily or every other day. Attention to the concentration of sodium, potassium, and chloride in the serum is needed when mercurial diuretics are used under these circumstances.

The carbonic anhydrase inhibitors such as acetazolamide (Diamox) are now used infrequently in view of the availability of chlorothiazide and hydrochlorothiazide. Carbonic anhydrase inhibitors result in selective excretion of sodium bicarbonate without effect on chloride, producing a variable degree of hyperchloremic acidosis.

Ammonium chloride is a diuretic agent which possesses two distinct disadvantages. It may be potentially damaging in liver disease, because of toxic properties of the ammonium ion, and the excess of chloride ions produces hyperchloremic acidosis. However, this excess of chloride ions may be of value because it effectively bolsters the chloruretic action of mercurial diuretics.

Chlormerodrin (Neohydrin), an oral mercurial diuretic and the aminouracil group of diuretics such as aminometradine (Mictine) have limited diuretic potency. Their use is frequently complicated by gastrointestinal side effects. Preparations of cation exchange resins do not, at present, enjoy wide use because of gastrointestinal side effects, problems of pallatibility, and limited effectiveness. The availability of chlorothiazide and hydrochlorothiazide has also reduced the need for these drugs.

Corticosteroids

A comment is in order on the possible usefulness of corticosteroids in the management of patients with progressive congestive heart failure. It is clearly recognized that the primary mineraloid effect of the adrenal steroids is the retention of sodium and the elimination of potassium.

The newer synthetic corticosteroids, however, such as prednisone and prednisolone, have a minor salt retaining action. The use of these newer agents in patients with refractory heart failure has been followed by striking, though usually temporary improvement after the usual diuretic measure had failed.[11,12] It is possible that their beneficial effects are related to inhibition of aldosterone activity, although this is as yet not corroborated. In carefully selected patients, prednisolone is used in doses of 5 mg four times daily.

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Value of Critical Slowing of Heart in Assessing Co-existence of Infarct with Bundle Branch Block: An Exercise in Electrocardiography

A 64 year old man was admitted with angina pectoris, recently increasing in frequency, severity and persistency. Electrocardiograms (Fig. 1) showed intraventricular block, presumably left bundle branch block, though this diagnosis could not definitely be made at this time because predominantly upright QRS complexes were not recorded in the usual six precordial leads. From a subsequent set of tracings (Fig. 3), however, the diagnosis of complete left bundle branch block was obvious. In Fig. 1 there was no R wave in Lead V_1; this deflection was very small in the entire remaining precordium. In many patients with left bundle branch block it is extremely difficult if not impossible to rule out the possibility of co-existent antero-septal myocardial infarct. Left bundle branch block alone, or antero-septal infarct alone, each is capable of decreasing the amplitude of the R waves or of eliminating R waves over the right precordium. In the present case, too, the small size of the R wave could be due to the abnormal direction of the forces activating the interventric-

FIG. 1

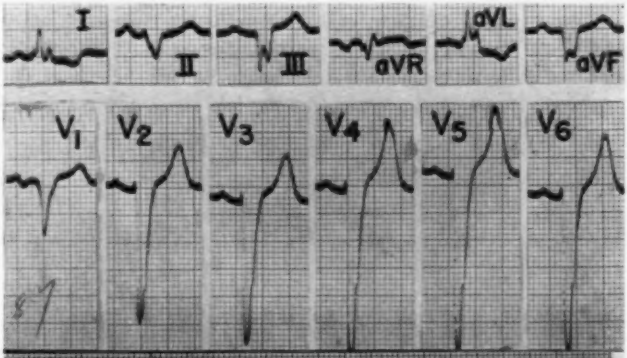

FIG. 2

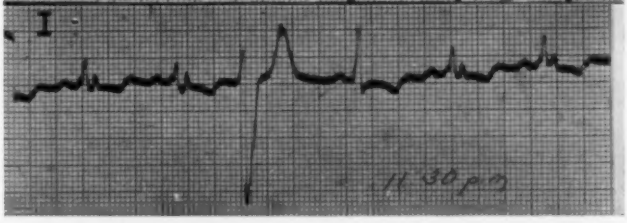

FIGURE 1. Intraventricular block, presumably left bundle branch block. QRS duration 0.15 sec. R wave absent in Lead V_1, small in Leads V_2 - V_6. Old antero-septal myocardial infarct cannot be excluded.

FIGURE 2. Lead I recorded at same time as Fig. 1, showing single ventricular premature beat followed by beat showing normal intraventricular conduction time. This was clue that intraventricular block was rate-conditioned.

ular septum as a consequence of left bundle branch block but co-existent old antero-septal infarct could not be excluded. A clue that might help resolve this problem was recorded in Figure 2 which was taken at the same time as Figure 1. It showed normal intraventricular conduction in the beat following a ventricular premature beat. This suggested that left bundle branch block might be a function of the heart rate and not a fixed phenomenon, or, worded slightly differently, that bundle branch block might be recorded only at heart rates exceeding a certain critical level and normal intraventricular conduction at rates below that level. The compensatory pause after the premature ventricular beat was regarded as being possibly long enough (rate slow enough) to fall below that level. It was therefore reasoned that if such a change in intraventricular conduction could occur spontaneously it might likewise be induced deliberately. To that end the right carotid sinus was massaged. It was found that, as is so commonly the case in coronary artery disease, the patient did indeed possess a sensitive carotid sinus.

The effect of stimulating the carotid sinus during each of the precordial leads was then recorded. Two observations were made. First, the maneuver induced atrial slowing and occasionally "dropped" ventricular beats (second degree atrio-ventricular block). Second, it shortened intraventricular conduction time to normal; the ventricular complexes remained abnormal in that they showed depressed RS-T segments and inverted T waves over the left precordium but the left bundle branch block had disappeared. But the most interesting finding was that now, with normal intraventricular conduction, the R waves had attained a respectable amplitude in the precordial leads so that old antero-septal infarct was not indicated in the electrocardiogram. It is ordinarily considered that if the R wave measures 2 mm. or more in amplitude in Lead V_2 and increases in amplitude to Lead V_4 it is reasonable to exclude this

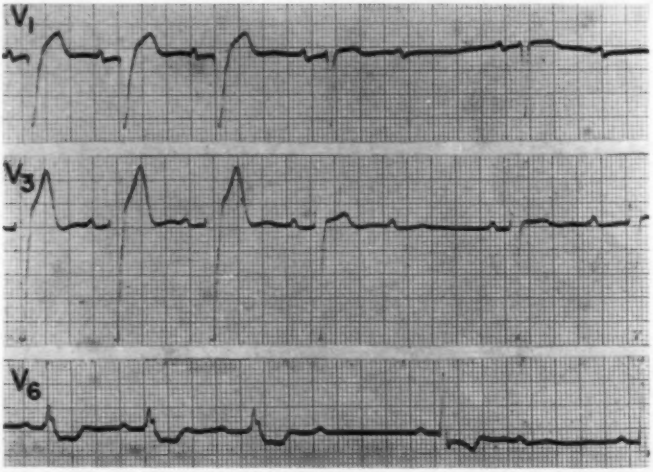

FIGURE 3. Leads V_1, V_3 and V_6 showing, initially, left bundle branch block then, as consequence of carotid sinus stimulation, sinus slowing and partial A-V block. The increased cycle length was associated with shortening of intraventricular conduction time to normal and increased amplitude of R waves. At this time it is clear that an electrocardiographic diagnosis of antero-septal myocardial infarct is not justified.

diagnosis. Therefore, whatever misgivings one might have on this score on clinical grounds and on the mere detection of left bundle branch block *per se*, the diagnosis of old antero-septal infarct could not be made on electrocardiographic grounds.

Ordinarily one thinks of aberrant ventricular conduction developing as a function of the heart rate when the heart rate becomes rapid, e.g. in the range encountered in clinical tachycardia. In the present case, however, the rate during normal conduction was 36, during left bundle branch block 75. Clearly the threshold between normal conduction and intraventricular block was between 36 and 75 per minute. A number of patients have now been observed in whom aberration developed at what is ordinarily regarded as a "normal" heart rate. Hence intraventricular block may still be a function of a faster heart rate even though the heart rate is still not rapid.

Deliberate slowing of the heart by carotid sinus stimulation has been useful in ruling in or out the diagnosis of antero-septal myocardial infarct in patients with left bundle branch block. It is recommended as a useful procedure.

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X-RAY FILM OF THE MONTH

Clinical Information

The patient is a 40 year old white man with signs and symptoms of superior vena caval obstruction. Swelling and cyanosis of the face and bulging of the eyes on bending were evident. These symptoms had been present for two years.

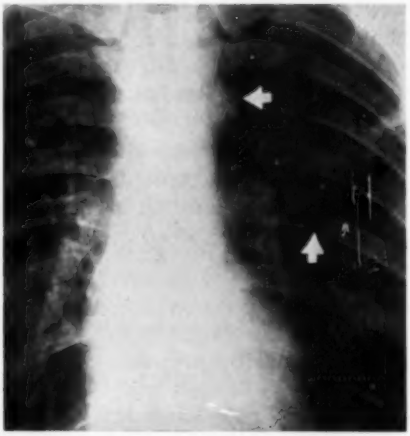

FIGURE 1. Chest roentgenogram. Note the rib notching (lower arrow) and the prominence along the superior mediastinum on the left (upper arrow).

Answer

Rib notching caused by dilated tortous intercostal *veins*, the result of obstruction of the superior vena cava from chronic fibrous mediastinitis, probably secondary to histoplasmosis.

Figure 2 shows a venogram, performed via the left antecubital vein. It reveals obstruction of the superior vena cava (arrow) above the entry of the azygos vein. There is extensive dilatation and tortuosity of the collateral veins. A very tortuous intercostal vein is seen eroding the under margin of the right fifth rib. At operation constriction of the superior vena cava by fibrous tissue was found.

Rib notching caused by intercostal venous dilatation was first reported in 1952 by McCord and Bavendam.[1] Their case was also caused by long-standing obstruction of the superior vena cava secondary to chronic fibrocalcific superior mediastinitis.

Coarctation of the aorta is, of course, by far the commonest cause of rib notching and until recent years was thought to be the sole cause of this roentgen sign. However, since 1937 a variety of other causes have been reported. These include:

1. Aortic insufficiency.

2. Hypertension with intercostal arteriosclerosis. In the above two conditions the notching was attributed to high pulse pressure in the intercostal arteries.
3. Intercostal neurofibromatosis.
4. Tetralogy of Fallot with collateral circulation to the lung via the intercostal arteries.[2]
5. Following the Blalock-Taussig operation.[3,4] The intercostal arteries, contributing collateral circulation to the arm, dilate on the side of the subclavian ligation.
6. Congenital absence of a main pulmonary artery.
7. Cavernous hemangioma of the thoracic wall.
8. Pulmonary arteriovenous fistula and arteriovenous aneurysm of the intercostal vessels.
9. Pulseless disease.

In all these cases the notching may be explained on the basis of local dilatation or tortuosity of intercostal arteries, veins, or nerves. Rib notching may be unilateral or bilateral, depending on the location of the underlying vascular process and the need for collateral circulation. Unilateral notching may also occur in aortic coarctation, on the right if the constriction occurs proximal to the left subclavian artery; on the left if there is an anomalous right subclavian artery arising distal to the constriction.

It is now believed that a high percentage of cases of chronic fibrosing mediastinitis with superior vena caval obstruction are sequelae of histoplasmosis. The mediastinal lymph node component of this disease may extend beyond the confines of the nodes into the mediastinal soft tissues producing fibrosis and calcification with compression of the superior vena cava.[5,6]

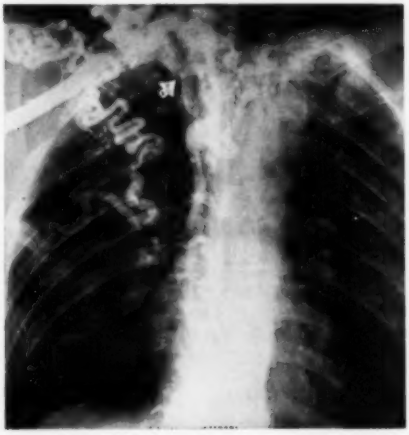

FIGURE 2

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Case Report Section

Some Cardiac Problems Presented by a Thymoma

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Although tumors of the thymus are rare, it is not unusual for them to simulate cardiac problems,[1] especially as otherwise unexplained cardiac enlargement. Most often enlargement is only apparent, the tumor being located in a position which roentgenographically cannot be separated from the cardiac silhouette. Such tumors rarely cause a cardiac murmur although a case was recently described in which a pulmonic systolic murmur vanished after removal of an anterior mediastinal Hodgkins' tumor.[2] At operation, the tumor was compressing the main pulmonary artery.

Recently, we examined a patient with a cardiac murmur and electrocardiographic changes due to intermittent compression of the pulmonary artery by a thymoma. The case was the more unusual because of the unique coexistence of thyrotoxicosis.

Case Report

A white woman, aged 52 years, was referred to the Ochsner Clinic on September 23, 1957 for advice regarding possible thyroidectomy. She first complained of nervousness and palpitations 18 months before admission. These symptoms became progressively worse and she was hospitalized in March, 1957, when she had atrial fibrillation with rapid ventricular response, as well as the usual signs of thyrotoxicosis; the protein-bound iodine determinations on two occasions were 15 and 13 gammas per 100 ml. and the basal metabolic rate was plus 20. A loud systolic murmur was noted at the base of the heart. She was given 10 mg. of mercaptoimidazole (Tapazola®) every six hours, with resultant improvement. In June, the protein-bound iodine value was 5 gammas per 100 ml.

When we first saw her, she looked perfectly well. She had no history of rheumatic fever, or of abnormalities in roentgenograms of the chest, and no knowledge of murmur before her physician's examination in March, 1957. The pulse rate was 80 beats per minute and regular, and the blood pressure 130 mm. Hg. systolic and 70 mm. Hg. diastolic. A stare and lid lag were still evident, but ocular convergence was normal. The thyroid gland was diffusely nodular and was estimated to weigh about 70 grams. The chest was slightly increased in postero-anterior diameter; a pulsation was noted in the second intercostal space 3.5 cm. to the left of the midsternal line.

Heart tones were of good quality; there was neither friction rub nor gallop. In the third left intercostal space next to the sternum, there was a grade four (Levine grading one to six) harsh systolic murmur, which was poorly transmitted; P_2 was slightly accentuated, being equal to A_2. On deep inspiration, with the patient supine, this murmur diminished considerably, and a deep breath while she was sitting caused it to disappear completely (Fig. 1). The murmur became louder on deep expiration with her in either position. There was no other murmur.

Results of routine laboratory examinations, as well as of thyroid function studies, were normal with the exception of roentgenograms of the chest and an electrocardio-

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gram. In an EPA roentgenogram, a mass was noted next to the main pulmonary artery which, on oblique views, proved to be in the anterior mediastinum. Its margins contained calcium (Fig. 2). At fluoroscopy cardiac size and pulsations were normal, as were the pulmonary vessels. There was no valvular calcification.

The electrocardiogram showed normal sinus rhythm, right axis deviation, and delayed activation of the right precordium presumed to be due to incomplete right bundle branch block (Fig. 3). Nonspecific ST-T changes in the left precordium were due to the digitalis that she had been taking.

A phonocardiogram recorded during normal respiration revealed the coarse systolic murmur in the pulmonic area (Fig. 1). Deep expiration intensified the murmur, and deep inspiration virtually abolished it.

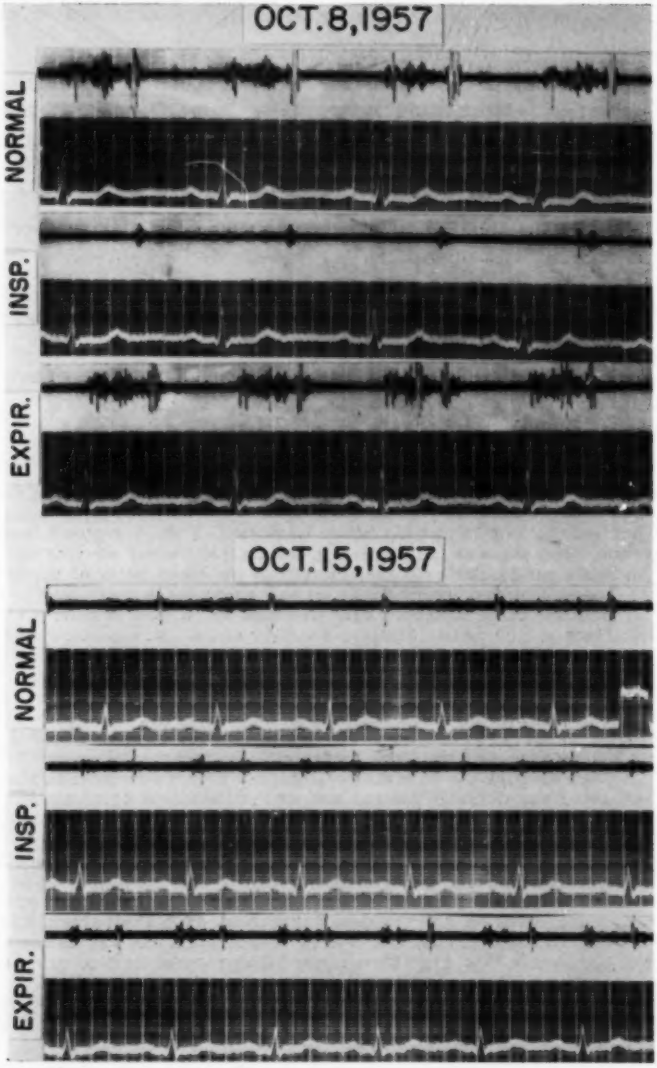
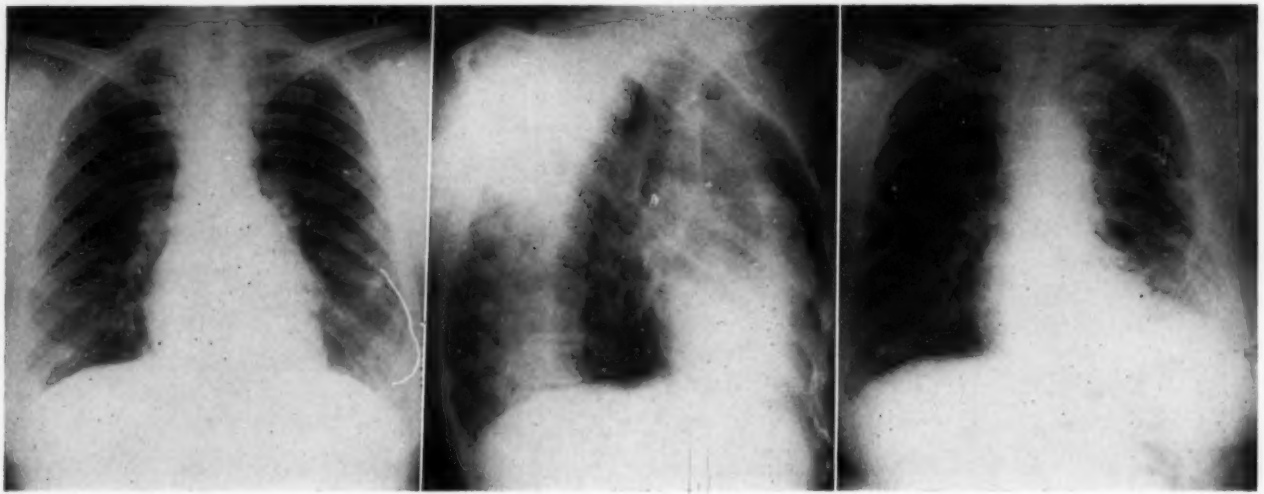


FIGURE 1: Preoperative and postoperative phonocardiograms. Note the remarkable respiratory variation of the systolic murmur preoperatively. All tracings were taken at the same microphone amplification. Legends along left margin refer to respiration.



2A 2B 2C

FIGURE 2: Preoperative erect postero-anterior (A) and right oblique (B) roentgenograms of the chest. (C) is a postoperative erect postero-anterior roentgenogram. Calcification is visible in the margin of the tumor in (A) and (B). Several small nodules containing calcium are present peripherally in both lungs.

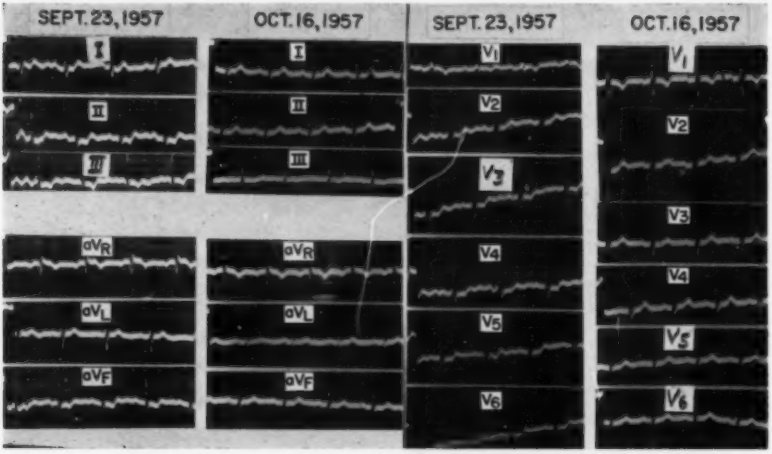


FIGURE 3: Preoperative and postoperative electrocardiograms. The delayed activation over the right precordium is no longer present postoperatively, and right axis deviation is gone.

Since she was euthyroid, the mediastinal tumor was considered a more urgent therapeutic problem than the thyroid, and after consultation with her physician and the patient, exploratory thoractomy was decided upon. At left thoracotomy on October 9, 1957, a large cystic mass was found in the anterior-superior portion of the mediastinum, extending down to the pericardium and up almost to the suprasternal notch. It was directly over the main pulmonary artery. After careful dissection, the mass was removed. She tolerated the procedure well.

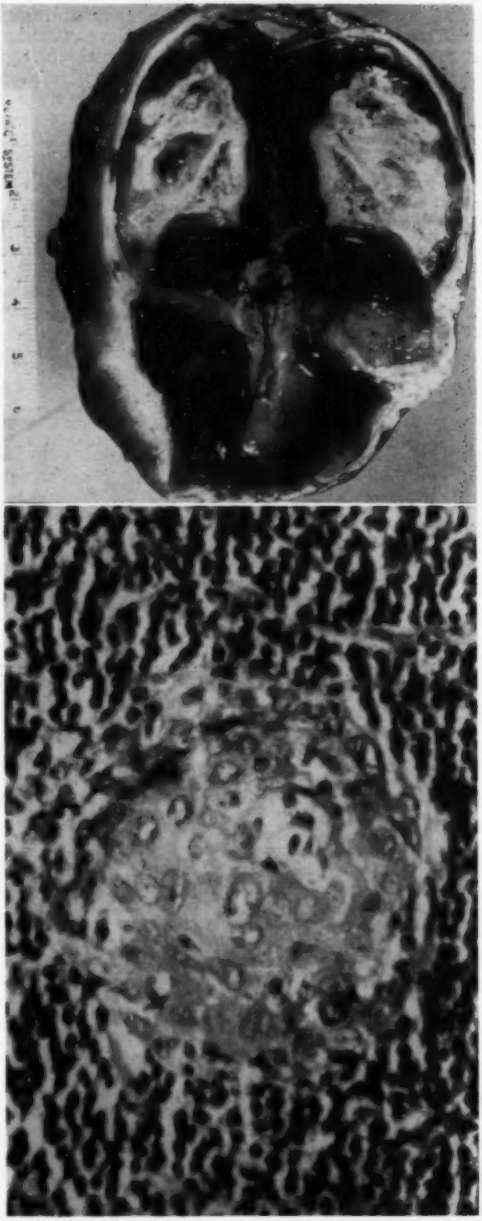
Postoperatively, the murmur almost disappeared, and the faint systolic murmur in the pulmonic area was unaffected by respiratory maneuvers (Fig. 1). In the electrocardiogram there now was no evidence of delayed right ventricular activity, the R-R' complexes in V_1 having been replaced by normal R-S relationships and the right axis deviation having reverted to normal (Fig. 3). At a later date thyroidectomy was performed without complication.

The excised cyst measured 9 by 4 by 4 cm. in its greatest dimensions, and its walls were greyish brown and yellow. On cut section the mass was filled with greyish-yellow, cheesy material, with some areas of calcification (Fig. 4A). On microscopic examination the wall of the cyst was found to be composed of dense hyalinized connective tissue with areas of foreign body giant cell reaction associated with cholesterol clefts and other vacuoles; also noted was calcified material and brown granular pigment suggestive of old hemorrhage. The appearance of sections from the body of the tumor was distinctive. The predominant cell was large with a uniform, oval, pale nucleus and a prominent nucleolus. These nuclei were surrounded by a syncytial mass of granular eosinophilic cytoplasm. In some areas distinct nests of lymphocytes were noted and in one section a small Hassall's corpuscle was present (Fig. 4B). The pathologic diagnosis was thymoma, epithelial type, with extensive fibrosis and cystic degeneration.

Discussion

Thymomas and other anterior mediastinal tumors may mimic primary heart disease in a variety of fashions. As in the present case, they may produce a murmur and electrocardiographic abnormalities. They may also falsely suggest cardiac enlargement. If malignant they may, of course, invade the heart itself.

In view of the intermittency of the pulmonic systolic murmur in this case, it seems reasonable to presume that compression of the pulmonary artery varied in degree with different phases of respiration as well as with different positions of the body. The location of the thymoma is consistent with this presumption, since the expanded intrathoracic space during deep inspiration, as well as when the erect or sitting position was assumed, must have provided for the heart more space in the mediastinum, which was being encroached upon by the tumor. The character of the murmur was



4A 4B

FIGURE 4: Gross (A) and microscopic (B) views of the tnymoma. A Hassel's corpuscle is shown in B.

unlike the functional murmurs audible in patients with thyrotoxicosis, and, moreover, the patient was euthyroid when we saw her. In cases with similar findings on routine examination, it is more important than usual to seek variability of the murmur with respiration and position of the body.

The changes that occurred in this patient's electrocardiogram are instructive. The initial changes (September 23, 1957) could have been caused by right ventricular hypertrophy, in view of the right axis deviation and incomplete right bundle branch block, and considering the clinical findings of a pulmonic systolic murmur and a mass adjacent to the pulmonary artery. Rapid regression of these electrocardiographic changes postoperatively (Fig. 3), however, make hypertrophy an unlikely explanation. It seems more plausible that the initial changes were due to a shift in both electrical and anatomical axis of the heart by the thymoma. Such a shift or displacement could also account for the right precordial R' wave, which most likely represented late terminal activity in the crista supraventricularis and pulmonary conus, rather than right bundle branch block.

Of incidental interest in this case is the unusual coexistence of thyrotoxicosis and a thymoma. In a recent review on thymic tumors[3] their common association with myasthenia gravis was mentioned and two instances of association with Cushings' disease have been reported, but there is no mention of thymic tumors associated with thyrotoxicosis. This association in the present case is more intriguing because of the absence of myasthenia gravis, a disease known to coexist with either thymoma or thyrotoxicosis alone.[4]

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Report of a Case of Proved Fulminating Hemophilus Influenzae Pneumonia in an Adult with Recovery

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This case is being presented because it is of more than usual interest for several reasons. It is a case of pneumonia caused by an unusual etiological agent, particularly in an adult.[1,2] It is a case of a pneumonia which was extraordinarily extensive and severe. In fact, it was so severe that several experienced observers who saw the patient are of the opinion that it was the most severe case of pneumonia with recovery that they had ever seen. Finally, this presentation is being made because it illustrates several very important practical points in the diagnosis and treatment of pneumonias in general.

This 46 year-old white man developed excruciating left chest pain 18 hours before admission to the hospital. This subsided spontaneously in a few minutes. Within a half hour, the pain recurred and it was accompanied by bright red hemoptysis and severe dyspnea. He was seen shortly after this by a surgeon who made a tentative diagnosis of pulmonary embolus and recommended immediate hospitalization. This was refused. No antibiotic was given. The patient continued to get more severely ill, developing chills, headache and cyanosis. On admission to the hospital, he was deeply cyanotic, dyspneic and in severe pain.

His blood pressure was 180 systolic, 70 diastolic. The temperature was 97.2°F., the pulse 112, respirations 30. Examination of the chest revealed dullness over the left lung base, and despite the extremely shallow respirations, some fine rales could be heard in this area.

The sputum specimen obtained at the bedside was thick, gelatinous and fleshy in consistency, and red. A direct smear revealed field after field of small, gram-negative rods. Culture yielded a pure growth of *Hemophilus influenzae*, type b. One of the initial blood cultures grew out *Hemophilus influenzae*, type b. On admission white blood count was 3500 with 51 per cent lymphocytes and 44 per cent neutrophiles. This count on the second hospital day was 3300. These were even more striking since he had been carefully followed during the previous year because of unexplained leukocytosis. On the third hospital day, the white blood count rose to 14,000; on the fourth day to 21,000; and on the fifth day to 28,000. It finally returned to 14,000 which had been his usual leukycyte count.

Acid-fast smears and cultures were negative. Cold, heterophile and all febrille agglutinations were normal. Agglutinations for murine typhus, rickettsial pox, Rocky Mountain spotted fever, influenza, types A, A-Asian strain, and B, and Q fever were negative.

He was placed on massive doses of antibiotics including penicillin, chloramphenicol and streptomycin. His temperature, which on admission had been subnormal, went to 101°F. within an hour or two, but only after antibiotics had been started, and after he had been placed in oxygen and given fluids. He improved until the sixth hospital day when he developed a full-blown case of delirium tremens. Associated with this was a spike of temperature, and a return of the severe air hunger and cyanosis. Despite the fact that oxygen was administered at the rate of 20 to 25 liters per minute, his respirations were as high as 45 per minute and the cyanosis increased.

The chest x-ray film (Fig. 1) taken within an hour of admission revealed a rather unusual diffuse, reticulating, and granular infiltration throughout the middle and lower portions of the left lower lobe. There was also patchy infiltration in the right lung base. The granularity was somewhat suggestive of interstitial pneumonia. On the second film (Fig. 2) there was seen marked progression of the pneumonia, with infiltration involving 80 to 90 per cent of his entire lung fields. There was also some fluid revealed, but most of the density was believed to be infiltration.

At this point, massive doses of oxytetracycline were substituted for the chloramphenicol in accordance with the results of the sensitivity studies, and the dosage of penicillin was empirically increased to 60,000,000 units a day by contiuous intravenous drip. His chest was tapped, and a small amount of purulent fluid was obtained, but this failed to grow an organism which is not surprising in view of the intensive antibiotic therapy. He remained critically ill for several additional days and then began to show gradual improvement. By the 30th hospital day, he was well with the exception of continued fever, averaging about 101°F. Antibiotics were discontinued,

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FIGURE 1: Chest x-ray film taken within hours of onset of first symptoms.

FIGURE 2: PA view of chest taken at height of illness.

FIGURE 3: Pleural reaction and scarring at the right base are all that remain in most recent follow-up film.

and the temperature returned to normal. We therefore concluded that the elevation of temperature at this point was due to drugs. He was discharged from the hospital on the 37th day, and now, almost a year later (Fig. 3), he is well. The most recent x-ray films revealed only pleural reaction and scarring at the left base.

The points that were of particular interest to us and the practical things that we can learn from this case are as follows:

(1) *Hemophilus influenzae* is an unusual cause of pneumonia at any age, but particularly in the adult.[1,2] In fact, in the 20 years prior to 1954, Crowell and Loube[1] found only three case reports in the American literature. Pure cultures of *Hemophilus influenzae*, type b from the sputum and the blood at the very onset, and the failure of extensive studies to reveal any co-existant etiological agent, are substantial proof of its causative role in this case, despite the known peculiarities of the *Hemophilus influenzae* organism.[3,4]

(2) This case points out the importance of withholding chemotherapy and antibiotic therapy in patients with pneumonia until cultures can be obtained, because of the resistance of some organisms to usual therapy, and, as in this case, unusual bacteriological agents can be responsible for the pneumonia. However, one should not wait in the seriously ill patient for the results of the bacteriological studies before beginning therapy.

(3) Initial leukopenia followed by leukocytosis is more common in *Hemophilus influenzae* infections.[1,5,6] However, any overwhelming bacterial infection can be ushered in with a marked leukopenia and normal temperature, and the finding of leukopenia and the absence of fever in a very sick patient with pneumonia does not necessarily imply that the pneumonia is of viral or rickettsial origin.

(4) This patient developed delirium tremens, a complication that has been seen so frequently in heavy drinkers with pneumonia. This should be anticipated in alcoholics who develop pneumonia and treated vigorously, because delirium tremens can be fatal, even without concomitant disease.

(5) This case also illustrates how the febrile period can be prolonged by the administration of antibiotics, particularly in massive doses.

(6) Finally, this case serves to emphasize the importance of a comprehensive approach to the patient severely ill with pneumonia including prompt etiological diagnosis, massive appropriate antibiotic therapy, intensive supportive measures, and prompt management of complications which are so frequent in overwhelming pneumonic infections.

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Intralobar Bronchopulmonary Sequestration of the Lung

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Intralobar bronchopulmonary sequestration of the lung is defined as a congenital cyst of the lower lobe of a lung occurring usually at the level of the diaphragm and receiving its arterial blood supply from the thoracic aorta.[1,2] Sequestration may be associated with diaphragmatic hernia (15-20 per cent).[3] The awareness and recognition of this condition with its aortic blood supply is of importance to the surgeon. These patients present themselves with unresolved pulmonary densities requiring exploration. Two additional cases of sequestration of the lung are presented.

Case 1: A 28 year-old white man was admitted to the University of Kansas Medical Center initially on October 3, 1954. Past history revealed recurrent febrile episodes involving the left lower lobe in 1944, 1949, and 1951. All of these illnesses responded favorably to antibiotic treatment. A chest x-ray film taken elsewhere one year prior to admission was stated to be normal. Ten days prior to admission he complained of left lower chest pain and a fever of 102°F. There was no cough. Prior treatment for three days with penicillin produced no improvement.

Physical examination revealed decreased expansion of the left lower chest. Breath sounds were absent over the left lower chest posteriorly with dullness over the same area. Laboratory findings were non-contributory except for a slight leukocytosis. Admission chest x-ray films showed left lower lobe consolidation and findings consistent with abscess formation. (Figs. 1, 2). Planograms of the area gave no further information. Bronchoscopy was negative.

On October 9, 1954, left thoracotomy revealed a sequestrated lobe, measuring 16 x 12.5 x 8 cm. Two aberrant arteries, measuring 0.5 and 0.6 cm., were identified as arising from the thoracic aorta. The venous drainage of the aberrant lobe was to the normal pulmonary vein. There was no communication with the lower lobe bronchus. Following removal of the aberrant lobe the patient had an uneventful course and was discharged on the eighth postoperative day.

Pathological examination of the surgical specimen revealed many communicating cysts containing purulent fluid. These cysts were lined with ciliated columnar epithelium. Alveolar walls were thickened. Sections of the arteries showed thickening of the walls with thrombosis and canalization. An acute pleural inflammatory reaction was present. An occasional surface bronchus was seen.

Case 2: A 13 year-old white boy entered the University of Kansas Medical Center for an initial admission on January 21, 1950. He complained of dyspnea and cramping left upper abdominal pain for one year. He stated that these symptoms seemed to have been aggravated following a football injury in November, 1949.

Physical examination revealed elevation of the left side of the diaphragm and the presence of bowel sounds on auscultation of the lower left chest.

X-ray films of the chest showed a density in the lower left chest with fluid and gas levels. An upper gastro intestinal series showed a large hiatal hernia with the stomach displaced into the left thorax (Fig. 2).

On January 25, 1950, left thoracotomy was done revealing herniation of the stomach, spleen and small bowel through a 5 cm. defect of the dome of the left diaphragm. In addition, an unsuspected 10 x 5 x 3 cm. aberrant lung lobe received its blood supply from the thoracic aorta. There was no bronchial communication of the lower lobe. The venous drainage was to the lower lobe. The diaphragmatic hernia was repaired and the aberrant lobe was excised.

Postoperative course was uneventful. Pathological examination of the specimen showed many dilated bronchi, thickened alveoli and atelectasis. The bronchi were lined with respiratory epithelium. The arteries were thick walled similar to those found in systemic organs rather than the pulmonary system.

Embryology. The pulmonary analage develops from the primitive foregut surrounded by the splanchnic plexus of capillaries. The developing lung bud on the ventral surface of the foregut carries part of the splan-

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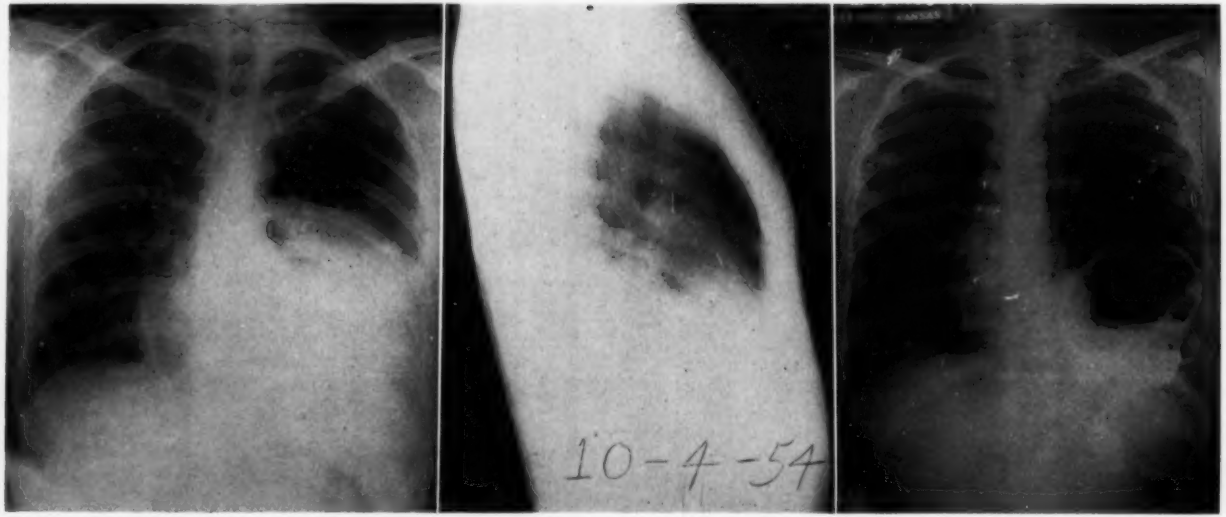

FIGURE 1 FIGURE 2

FIGURE 1: Pre-operative AP and lateral chest x-ray film showing left lower lobe consolidation. **FIGURE 2**: Barium study revealing diaphragmatic hernia and an unsuspected pre-operative aberrant lobe.

chnic plexus along with it. The dorsal and ventral portions of the aorta supply the lung until the 8 mm. stage. Normally the primitive pulmonary arteries anastomose with the plexus on the lung bud and the aortic connections atrophy. A remnant of the fifth aortic arch may persist, resulting in the development of a sequestrated lung. The vascular theory seems to correlate best with pathological findings.[4,5]

Other etiological factors such as mechanical traction due to deepened fissures or pressure from anomalous vessels have not proved consistent with embryonic or pathologic studies.[6] Oxygenated blood under aortic pressure through persisting anomalous arteries may be responsible for the fibrosis and cyst degeneration.

Diagnosis. The most common presenting symptoms are chronic and recurring productive cough, chills, fever or chest pain. This nondescript symptomatology can be confused with unresolved pneumonia, lung abscess, empyema, bronchiectasis, or an infected congenital lung cyst. The usualy history is one of a course of antibiotic treatment giving relief during the infectious phase only to have a recurrence of symptoms at a later date. The source of infection to a sequestered lung is hematogenous or spread from an adjacent pneumonitis. Infection via the bronchial tree occurs only when communication is present (17 per cent).[7]

X-ray films of the chest usually reveal a sharply outlined posterior medial density lying in the inferior portion of the lower lobe. Either side may be involved with a slight preponderance on the left. Single or multiple cystic areas may be visible or obscured by consolidation of an infected surrounding lung.[8] Both air and fluid may be present depending on bronchial communication. Planograms of the involved lung arear may be helpful. Bronchograms will outline the mass or fill the bronchi, depending on bronchial patency. Aortography has been suggested as an aid to the diagnosis. However, this would preclude an awareness of the diagnosis.[9]

Pathological Findings. The resected lobe may contain single or multiple cysts or ectatic bronchii. The cysts are lined with respiratory epithelium and often filled with mucoid material.[10] The venous drainage is usually via the pulmonary vein. In the presence of infection, abscess formation is present. Atheromatous changes in the arteries may be present reflecting changes due to increased aortic blood flow.

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Eosinophilic Granuloma of the Lung

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Introduction

Eosinophilic granuloma limited to the lung was first described in 1951 when Farinacci[7] reported two patients diagnosed by lung biopsy. Since then, 14 more cases have been reported: five by Arnett and Schulz,[1] three by Auld,[2] two by Mazzitello,[19] and single cases by Virshup and Goldman,[26] Thompson,[25] Livingston,[16] and Kaunitz.[11] It is our purpose to add two cases of our own and briefly review the literature.

Case 1. A 38 year-old white woman was first seen in September, 1955 with a nine-month history of coughing which was productive of one half cup of clear sputum daily. There was no other symptom. Physical examination was essentially normal. A chest roentgenogram demonstrated diffuse bilateral nodular infiltration with evidence of fibrosis and emphysema (Fig. 1). The hemogram and urinalysis were normal. There was no eosinophilia. Pulmonary function studies were normal. A lung biopsy was accomplished with a preoperative impression of sarcoidosis. No pleural adhesions or subpleural blebs were present. No mediastinal adenopathy was noted. Multiple 2 to 4 mm. nodules were present throughout the lung parenchyma. The pathological diagnosis was eosinophilic granuloma (Fig. 2). Only general supportive treatment was given, but her family doctor reported that she was completely recovered two months after surgery and has remained well.

Case 2: A 37 year-old white woman was first seen in November, 1957, with a five-month history of malaise, slight weight loss, and low-grade fever. She had been treated with broad spectrum antibiotics without improvement. She developed vague anterior chest pain, but had no cough or night sweats. Physical examination was essentially normal. A chest roentgenogram showed a diffuse nodular bilateral infiltrate similar to that in Case 1. The hemogram was normal and eosinophils ranged from 0-3 per cent. Laboratory examinations, including stool studies for parasites and tuberculosis smears and cultures, were negative. Scalene lymph node biopsy was negative. A right pulmonary biopsy was performed and the findings and diagnosis were essentially similar to Case 1. No specific treatment was instituted, but she became asymptomatic. Over a period of six months, the x-ray appearance of the lungs gradually improved.

Historical

In 1940, Otani and Ehrlich[20] and Lichtenstein and Jaffe[15] independently described eosinophilic granuloma of bone. Otani and Ehrlich called it "solitary granuloma of bone" and thought that it was due to trauma. The other two authors gave it its present name and proposed a viral etiology. In 1941, Farber[6] suggested that eosinophilic granuloma of bone, Hand-Schüller-Christian disease, and Letterer-Siwe disease were variations of the same basic disease process. This view has become generally accepted.[5,10,17] Lichtenstein[14] has proposed the term "Histiocytosis X" to include eosinophilic granuloma, Hand-Schüller-Christian disease and Letterer-Siwe disease. He suggests that eosinophilic granuloma confined to the lung is actually an early expression of Hand-Schüller-Christian disease and predicts the subsequent development of other visceral or skeletal lesions. It is of interest, however, that such progression has not yet been reported although lung and bone lesions have occurred simultaneously.[4,9,13,18,27]

Review of All Cases

The case reported by Kaunitz[11] is not included, as it differs greatly from the others both radiologically and clinically. Thus, 17 cases are available for analysis.

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The typical radiographic appearance is that of a diffuse, bilateral, nodular infiltrate (Fig. 1). Associated areas of emphysema and fibrosis have given rise to the term "honeycomb lungs" found in British literature.[8,21] The symptoms are generally mild. The common complaints in order of frequency are cough, weight loss, malaise, chest pain, low-grade fever, and dyspnea. Pneumothorax, which occurred in two cases, can be explained by the occasional surgical findings of subpleural blebs and cysts.

Laboratory findings are nonspecific. A mild eosinophilia, ranging from 5-10 per cent, was present in four of the 17 patients. The sedimentation rate was elevated in six of the seven cases in which it was reported. The A/G ratio was occasionally reversed. Pulmonary function studies were essentially normal in the few cases so studied. Scalene node biopsy was negative in all nine cases in which it was performed.

The condition is more prevalent in men by a ratio of 14 to 3. Ages ranged from 15 to 52 years with all but three cases being between 20 and 40. All but one were Caucasians. Four were treated for tuberculosis before the correct diagnosis was established by biopsy.

The pathological picture is quite constant. The pleura is usually free although in three cases minimal adhesions were present. On palpation, the lung parenchyma is studded with disseminated 2 to 15 mm. nodules. These are firm, and on cut section appear grayish white or tan. Hilar lymph nodes are not prominent. Microscopically, the lesions appear

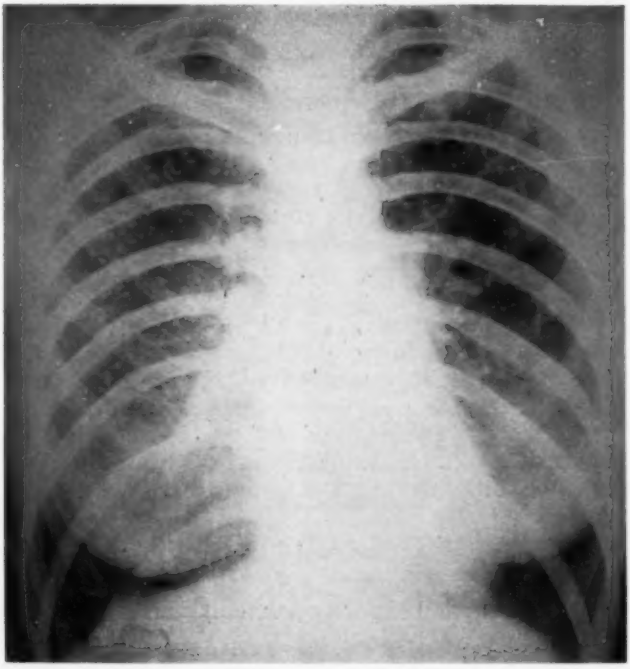

FIGURE 1: Case 1. Chest roentgenogram showing the typical bilateral nodular infiltrate of eosinophilic granuloma with areas of emphysema and fibrosis.

as granulomas consisting of masses of histiocytes throughout which varying numbers of eosinophiles are scattered (Fig. 2). Macrophages laden with brown pigment granules are often found in large numbers in the adjacent uninvolved alveoli.

There is no generally accepted method of treatment. Antibiotics were used without demonstrable benefit in four of the 17 cases. Irradiation was employed in four with questionable benefit, although the chest x-ray showed fairly rapid clearing in one. Cortisone or ACTH was used in eight. No improvement was noted in three, prompt remission occurred in two, and gradual improvement over a period of months occurred in three. Only general supportive treatment was given to nine patients all of whom slowly improved. Most cases have become asymptomatic with or without treatment and in none have symptoms progressed. It should be noted that in several patients more than one form of treatment was tried.

Discussion

The etiology of eosinophilic granuloma of the lung remains unknown. Due to its histologic similarity to eosinophilic granuloma of bone, it has been assumed that they have a common origin. Cases have been reported with typical lung lesions in which bone lesions were also present.[4,13,18,27]

Auld[2] has noted a proliferative endarteritis in his and in Farinacci's cases. He postulated a hypersensitivity state to explain both the arteritis and eosinophilic infiltration. He proposed a possible relationship to Loeffler's syndrome and periarteritis nodosa. A mild endarteritis was noted in three other cases but was not considered to be significant.[1,2,25] No evidence of it was found in the present two cases. Thus endarteritis was present to some degree in eight cases and either absent or not mentioned in nine cases. The relationship of Loeffler's syndrome and periarteritis nodosa to hypersentivity has been stressed by others.[9,23,24]

Clinically and radiologically eosinophilic granuloma of the lung and Loeffler's syndrome are quite dissimilar. The former is an entity of benign symptomatology, roentgen findings of diffuse bilateral nodular infiltration and a normal or minimally

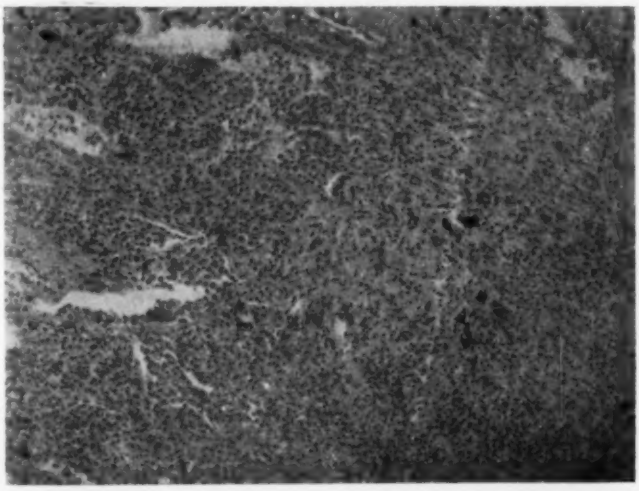

FIGURE 2: Case 1. Portion of a nodule of eosinophilic granuloma. The figure reveals almost complete obliteration of pulmonary architecture with only a few alveolar spaces recognizable. In the area of obliteration, alveolar septa and lumen are infiltrated with innumerable cells of essentially two types: macrophages and eosinophiles. The macrophages, or histiocytes, are seen as large poorly demarcated cells with much cytoplasm and with pale round or oval nuclei. The smaller denser cells intervening between the macrophages are eosinophiles. (100 X)

elevated eosinophile count. Loeffler's syndrome is characterized by more severe symptoms, roentgen findings of transient, migratory pneumonic infiltrations (Fig. 3), and greatly elevated eosinophile count of 15 to 60 per cent.

The case reported by Kaunitz[11] presented clinically and radiographically as Loeffler's syndrome. Microscopically, however, in addition to the eosinophilic pneumonia there were areas of typical eosinophilic granuloma. Buckles[12] case of Loeffler's Syndrome also showed areas of granuloma as well as pneumonia. The microscopic slides have been reviewed by the authors and the presence of granulomatous areas was confirmed (Fig. 4). Furthermore, although there was definite circulating eosinophilia, the area of infiltration failed to migrate and a pneumonectomy was performed for suspected carcinoma. The granulomas in those two cases were microscopically indistinguishable from those in eosinophilic granuloma. We have recently biopsied two cases of clinically classical Loeffler's syndrome. One, biopsied in the acute phase, showed a typical eosinophilic pneumonia (Fig. 5). The other, biopsied late in the healing stage, showed localized areas of eosinophilic granulomas (Fig. 6). These findings suggest the possibility of some fundamental relationship between all these conditions.

Another condition that may belong in this general group is "tropical eosinophilia," which is common in India. This entity, of unknown etiology, is characterized by roentgen findings similar to those of eosinophilic granuloma of the lung and by a markedly elevated circulating eosinophilia. To our knowledge biopsy studies have not been reported but it is suspected that the findings would be similar to those in eosinophilic granuloma. The present terminology may have to be revised as more is learned about this interesting group of possibly related conditions. Reeder and Goodrich[22] have proposed the more inclusive term of "pulmonary infiltration with eosinophilia (PIE syndrome)."

The differential diagnosis of eosinophilic granuloma of the lung should include sarcoidosis, the pneumoconiosis, fungus diseases suuch as coccidiodomycosis or histoplasmosis, lymphomas, scleroderma, periarteritis nodosa, Loeffler's syndrome, fibrocystic disease of the pancreas and the disseminated forms of Histiocytosis X. Most of these can be readily ruled out by the history, physical findings, and appropriate laboratory tests. However, if the diagnosis remains in doubt one should not hesitate to obtain a lung biopsy. This may be readily obtained either through a posterolateral approach or by way of the anterior intercostal method of Klassen.[12]

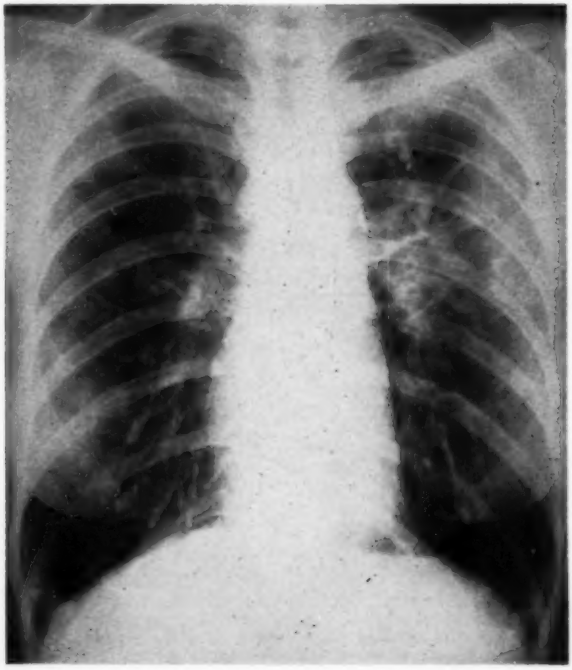

FIGURE 3: Chest roentgenogram of case of Loeffler's syndrome (proven by biopsy), showing patchy pneumonic infiltrate.

FIGURE 4

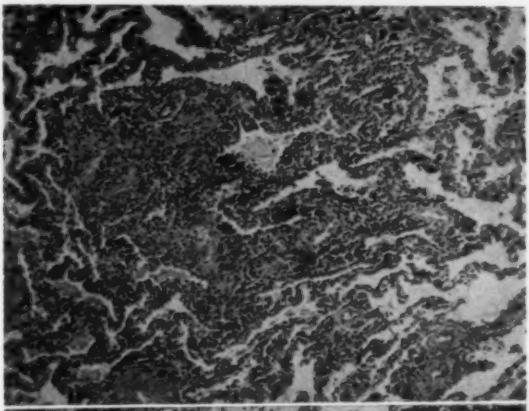

FIGURE 5

FIGURE 6

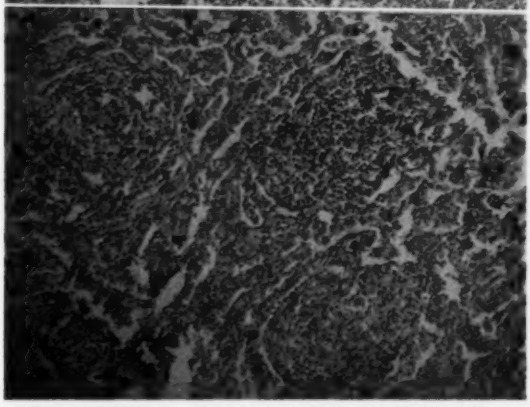

FIGURE 4: Loeffler's syndrome (Buckles[5]). The area illustrated contains a zone of pneumonic consolidation consisting almost entirely of small cells with dense nuclei which are eosinophiles although the granules are not recognizable at this magnification. At the top center and lower right are small areas of granulomatous inflammation with infiltrating macrophages and scattered eosinophiles. (100 X)

FIGURE 5: Loeffler's syndrome, acute stage. The figure shows a large area of pneumonic consolidation by small cells with dense nuclei virtually all of which are eosinophiles. Note also a moderate perivascular adventitial infiltration by eosinophiles. (100 X)

FIGURE 6: Loeffler's syndrome, late stage. In this case pneumonic consolidation has completely disappeared but there is thickening and infiltration of alveolar septa and perivascular areas by small cells with dense nuclei, eosinophiles. Among the eosinophiles are scattered larger infiltrating macrophages or histiocytes. The resemblance betwen this appearance and that characteristic of eosinophilic granuloma is apparent. (100 X)

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Unusual Coin Lesion in the Lung*

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It is generally agreed that so-called coin lesions of the lung should be resected regardless of the result of clinical and laboratory studies. The removal of malignant tumors in an early stage far out-weighs in importance the small surgical risk taken by the patients with benign coin lesions. This report calls attention to one of the rare malignant tumors in this group.

Case Report

A.S., a 52 year-old white clerk, was admitted to the hospital on March 7, 1958. During a routine examination at his place of employment, a roentgenogram of the chest showed a mass in the left hemithorax. He had a slight non-productice cough which had not changed during the past several years. There was no history of chest pain, hemoptysis, night sweats or dyspnea on exertion. He had smoked approximately one pack of cigarettes daily for 30 years.

In January, 1946, following complete extraction of his teeth, he noted a mass in the right cheek which was aspirated and disappeared. Approximately two months later, he noted a recurrence of the mass which was asymptomatic. In April, 1946, at a local hospital, the mass was described as being situated at the region of the trunk of the right facial nerve, having the size and shape of half an egg, solid and attached firmly to the deeper tissue. The mass was removed under local anesthesia and was described as a spheroid tumor measuring 3 x 3 x 2½ cm., soft, solid, apparently encapsulated, mixed grayish-white and red, and believed to be a carcinoma.

The tumor continued to grow and, in October, 1947, at the same hospital a mass measuring 4.5 cm. x 7 cm. in the right parotid region was described. He received x-ray therapy to the mass, 3000 r in air, through a single port, during the months of October and November, 1947. The mass regressed in size and in February, 1948 measured 3 x 4.5 cm. An additional 2000 r in air was administered February and March, 1948.

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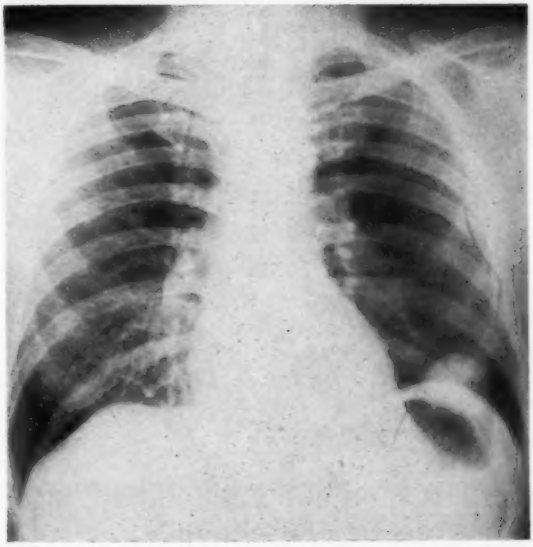

FIGURE 1: Note circumscribed mass in left lower lung field.

The lesion persisted, and in October, 1948, he was seen at the Memorial Center for Cancer and Allied Diseases in New York City. A subtotal parotidectomy was performed. The pathological report was malignant mixed tumor. He remained free of disease until June, 1951, when he returned to the Memorial Hospital with three nodules in the previous operative site. One of these was excised under local anesthesia. The pathological report described radiation dermatitis and ulceration. The wound healed well and there was no further swelling. He continued to do well until 1958 when the x-ray film examination of his chest revealed the mass mentioned above.

On admission to the hospital, his temperature was 98°F, pulse 72, blood pressure 146/105, weight 161 pounds. Physical examination was within normal limits except for the presence of a well-healed scar in the right parotid region with no evidence of adenopathy. The blood count and urinalysis were within normal limits. The blood urea nitrogen was 9 mgm. per cent, total protein 7.2 grams per cent with 3.7 grams per cent albumin, and 3.5 grams per cent of globulin. The platelet count was 360,000 per cu. mm. Repeated smears and cultures of the sputum for acid-fast bacilli were negative. An electrocardiogram was within normal limits. Roentgenologic examination of the chest (Fig. 1) revealed an abnormal density just above the left leaf of the diaphragm indicating a possible pedicle and attachment to the diaphragm. Intravenous and retrograde urograms and an upper GI series were within normal limits. Bronchoscopy showed no abnormality, and malignant cells were not found in bronchial washings.

On April 3, 1958, left thoracotomy was performed under general anesthesia. A mass measuring 4 cm. in diameter was noted in the left lower lobe. The remainder of the lung and hilum were normal. Wedge resection was performed. He had an uneventful postoperative course and was discharged April 18, 1958. Since that time, he has been followed at regular intervals. In April, 1959, he was well, had gained six pounds and roentgenograms of the chest showed no abnormality.

The specimen was a wedge shaped lung resection (Fig. 2). Attached to a rim of pale, atelectatic lung tissue about 1 cm. wide, was an ovoid mass, 4 cm. in diameter, covered by a glistening translucent capsule and appearing cystic to the touch. On incision, however, it was solid, though soft, and pale brown. It had a tendency to shell off the adherent lung tissue. Grossly, a lymphoma was considered as a possible diagnosis. On frozen section, no definite identification was possible.

Microscopically, the tumor was not encapsulated, but had merely compressed the surrounding lung tissue. It consisted of small dark staining cells mostly taken up by the hyperchromatic large nuclei. These cells were mostly bipolar and curled giving the entire mass a whirl-like appearance. Some of the nuclei were oversized. There was a rare mitosis and an occasional multinucleated cell. There were within the tumor at one point a well formed small bronchiole and larger and smaller vascular areas showing lymphoid tissue (Fig. 3).

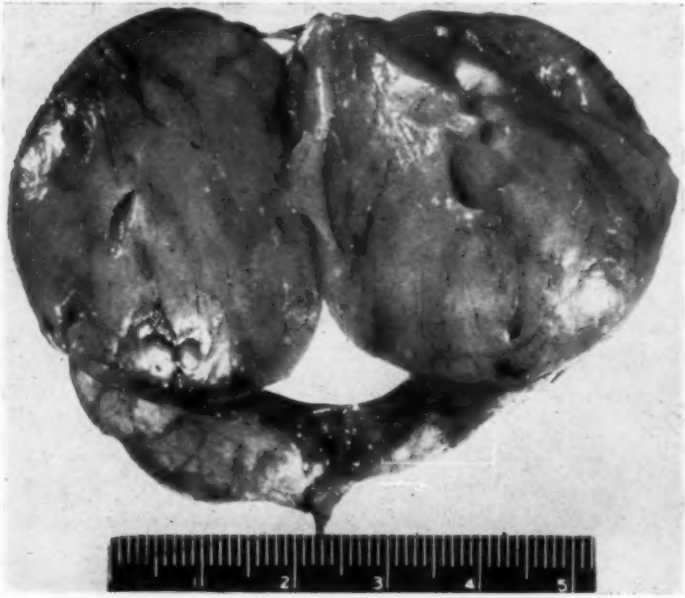

FIGURE 2: Cross section gross specimen.

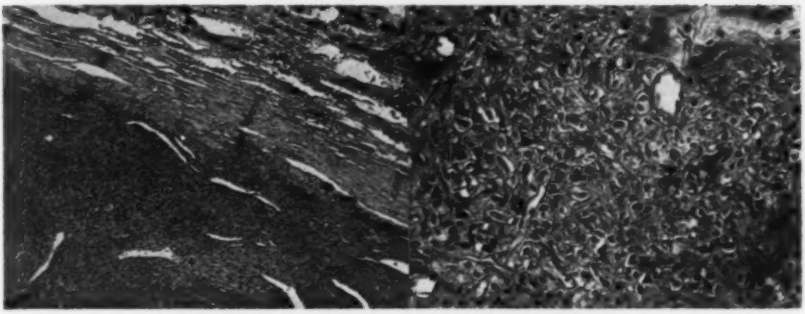

FIGURE 3A: Microscopic appearance (H&E, 40x)

FIGURE 3B: Microscopic appearance (H&E, 180x)

A microscopic section of the tumor removed at the Memorial Hospital in New York, loaned to us through the kindness of Dr. Frank W. Foote, Jr., showed a definite similarity with our specimen. Thus, the diagnosis of malignant mixed tumor of parotid, metastatic to lung was established.

Discussion

Storey[1] has suggested criteria for the application of the term "coin lesion:" (1) one to five cm. in size, (2) round or oval in shape and sharply circumscribed borders, (3) surrounded on all sides by normal appearing lung, (4) producing no symptom, (5) homogenous in density or containing calcium and (6) solitary.

Hood[2] reported 156 patients in whom resection had been carried out for solitary circumscribed lesions of the lung. Twenty-five (16 per cent) were primary bronchogenic carcinoma and seventeen (10.9 per cent) were either metastatic sarcoma or carcinoma.

Jones[3] reviewed 714 histologically proved cases of solitary circumscribed lesions of the lung reported in the literature. One-hundred ninety (26.6 per cent) were primary bronchogenic carcinoma and 30 (4.2 per cent) were metastatic malignant tumors.

It should be noted that reports deal only with resected lesions rather than the total number of coin lesions observed. It would appear that the most important factor in the treatment of coin lesions is the attending physician's decision that a particular lesion does not warrant surgical exploration. Other factors are the patient's refusal of operation and his general state of health. A long-term follow-up of coin lesions not submitted to exploration would be of great value in determining the true incidence of malignant disease.

Histologically benign mixed tumors of the parotid do not metastasize, though one notable exception to this rule reported by Foote and Frazell[4] should be recalled. In this instance, an oval lesion of 2.5 cm. maximal diameter occurred in the left lower lung of a young woman, seven years after the last removal of a recurrent "benign" mixed tumor of the parotid. The lung lesion was histologically identical with the local tumor.

Though malignant mixed tumors are known to cause distant metastases in one-third of the cases, the long interval between our patient's last local manifestation and the occurrence of the lung tumor is remarkable.

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Simultaneous Tuberculosis and Coccidioidomycosis in an Asymptomatic Patient

CASE REPORT

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It would seem to be a rare occurrence for culture proved coccidioidomycosis and culture proved tuberculosis to exist in the same segment of lung at the same time. The following is a case report in which this occurred.

A 37 year-old attorney was seen by an internist in May, 1959 for a routine examination. There was no symptom referrable to the heart or lungs except a "smoker's cough" which had ben present for many years and which was not considered important by the patient.

Past history revealed only that there had been a vas ligation and that in November and December, 1958 several teeth were pulled in the face of fairly severe gingival infection, but this was not followed by any pulmonary symptom or submandibular or cervical lymphadenopthy. System review revealed that in addition to the smoker's cough, he had a constant stuffiness in his head with some postnasal drip which he characterized as sinusitis, but for which he had sought no treatment. He had used a great deal of alcohol recently and had smoked heavily for over 20 years. There was no history of wheeze, hemoptysis, fever, or weight loss.

Physical examination revealed excellent pulmonary function and no abnormality.

Chest x-ray films revealed a mass the size of a lemon in the upper lobe of the left lung. Our first impression of this was that it represented an indolent interstitial pneumonitis with possible abscess formation because of its fuzzy borders and center. We could not relate it to the dental surgery done six months previously. He was placed on tetracycline for two weeks, after which re-examination revealed no change in the mass. Because of the possibility that this might be a tumor, resection was recommended.

On May 26, 1959 left upper lobectomy was done. The findings at the time of operation were those of a hard mass with some evidence of "daughter granulomas" around its periphery. The lobe came out cleanly, without evidence of hilar involvement and with no technical difficulty. The postoperative course was uneventful.

Examination of the specimen revealed a multinodular mass, the largest nodule having a necrotic center containing caseous material. Histologic sections revealed tubercles with caseation and many acid-fast bacili were seen in the specially stained tissue sections.

FIGURE 1
FIGURE 1: Preoperative film.

FIGURE 2
FIGURE 2: Preoperative planigram.

FIGURE 3
FIGURE 3: Postoperative film.

Bacteriologic study of the resected speciment revealed the following:

1. Positive for acid-fast organisms typical of Mycobacterium tuberculosis on direct smear.

2. June 25, 1959: Sabouraud's Culture, Coccidioides immitis.

3. July 2, 1959: Acid-fast bacilli seen on Petragnani medium, having the cultural and morphological characteristics of Mycobacterium tuberculosis.

Our laboratorians feel that both of these cultures are valid and that this represents a true instance of simultaneous coccidioidomycosis and tuberculosis in the same persons.

He is on antimicrobial drugs and has been allowed limited activity. He is asymptomatic and his x-ray films are now clear.

ADDENDUM

Since this paper was accepted for publication we have learned of two other cases which have been reported in a paper entitled "Nodular Pulmonary Granulomas: A Pathologic Study of 144 Cases" by Dr. Vern R. Waldorf and Dr. J. B. Hutcheson, to be published in the *American Review of Respiratory Diseases*.

The So-Called Leukemic Lung

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Leukemic infiltrations in the lungs are particularly well known to anatomicopathologists.[5,8,9,12] Bötcher[3] first called attention to them in 1866. The infiltrations are most frequently located in the region of the interlobular fissure, the intrapulmonary lymphatic nodes, the bronchi, or the peribronchial and perivascular connective tissue. In some cases, they have been observed in the pulmonary alveoli or vessels as thrombi or emboli.

In life, they are seldom diagnosed on account of their atypical clinical symptoms and x-ray film shadows. In the majority of cases, especially acute leukemia, changes in the lungs appear only toward the end of life, when x-ray film examinations have been discontinued on account of the condition of the patient. On the other hand, changes which can be ascertained anatomically are often unrecognizable either clinically or radiologically.

It was only in 1927 that Joachim and Loewe[11] observed a case of myeloblastic acute leukemia in which x-ray film examination showed spotty shadows in both lungs. The clinical symptoms consisted of dyspnea and periodic expectoration of bloodstained sputum. Anatomical examination showed subpleural infiltrations 2 - 5 cm. in diameter. Histological examination revealed infarcts as a result of the blockage of the vessels by emboli composed of myeloblasts.

Since 1927, interest of clinicians and radiologists in changes in the lungs during the course of leukemia has increased as shown by reports in the literature.[2,4,7,10,13,15]

The clinical picture and physical signs are variable and do not correspond to the radiological changes.

X-ray films show either disseminated miliary foci or limited tumor-like bands of infiltration, simulating pictures corresponding to lobular or bronchial pneumonia or to tumors of the mediastinum or hili. Larger infiltrations may undergo softening, with formation of cavities. Fiessinger[6] considers the cavities the result of autolysis caused by the action of the proteolytic ferments of the myelocytes. The changes in the lungs may be associated with foci of atelectasis, unspecific inflammatory changes and stagnation. Infiltrations may be partially or entirely invisible as a result of the accumulation of transudate or effusion in the pleura, causing thickening, adhesions or fibrinization. Adlercreutz and Bergendal[1] observed a relation between the radiological picture and the general condition of the patient. An improvement in the blood picture was accompanied by regression of the pulmonary infiltrations. Moeschlin[12] described a case of acute paramyeloblastic attack in the course of chronic myeloid leukemia with miliary pulmonary infiltrations, which regressed during a period of remission.

Diagnosis may be established only on the basis of a confrontation of the radiologic picture of the lungs with the clinical symptoms and

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hematologic examinations. In the differential diagnosis, pneumonia, tuberculosis and other infective diseases of the lungs (bacterial, rickettsiosis, parasites, virusal), benign and malignant neoplasms should be taken into consideration. Disseminated miliary foci should be differentiated from the pulmonary changes seen in the course of erythematous lupus. The differentiation between leukemia with pulmonary infiltrations and the leukemic reaction in tuberculosis or carcinoma may be difficult.

Falkenstein and Fowler[6] ascertained leukemic infiltrations in the lungs in 8 per cent and pleural effusions in 6.5 per cent of cases of acute lymphatic leukemia in children. Kirschbaum and Preuss[13] observed leukemic infiltrations in the lungs in 13 per cent of 125 cases of chronic lymphatic leukemia.

In the available literature, I have not found a description of a case of chronic myeloid leukemia with pulmonary changes of an infiltrative and cavernous character, hence, this report.

Case History

H. F., a woman of 41 years, (no occupation) reported September 17, 1953 with a tumor in the abdominal cavity and general debility. In August, 1949, she had been in a sanatorium for tuberculosis because of an infiltration in the upper lobe of the right lung. No Koch's bacilli had been found in the sputum. Pneumothorax had been kept up for a period of about two years. In May, 1952, her condition deteriorated. The tomographic picture showed a cavity, but Koch's bacilli were not found in the sputum. She was again sent to a sanatorium where she received streptomycin, and was discharged improved.

She was alert and could lie in any position. Her skin and mucous membranes were pale, and the subcutaneous fatty tissue was poorly developed. Lymph nodes were not palpable. Lungs: in the right supraclavicular, supraspinal and scapular regions numerous consonating medium and small rales could be heard. Bronchial respiratory notes were normal over the whole of the lungs. There were no abnormal cardiac findings. The pulse was moderate, pressure normal, 108/min. and the blood pressure 130/75 mm Hg. The lower margin of the liver was two fingers below the right costal arch. The spleen extended almost to the symphysis pubis and mid-line.

Supplementary examinations: Hemoglobin 46 per cent, erythrocytes 3,200,000, leucocytes 256,000 per mm^3, color index 0.72. Leucocyte count: myeloblasts 3 per cent;

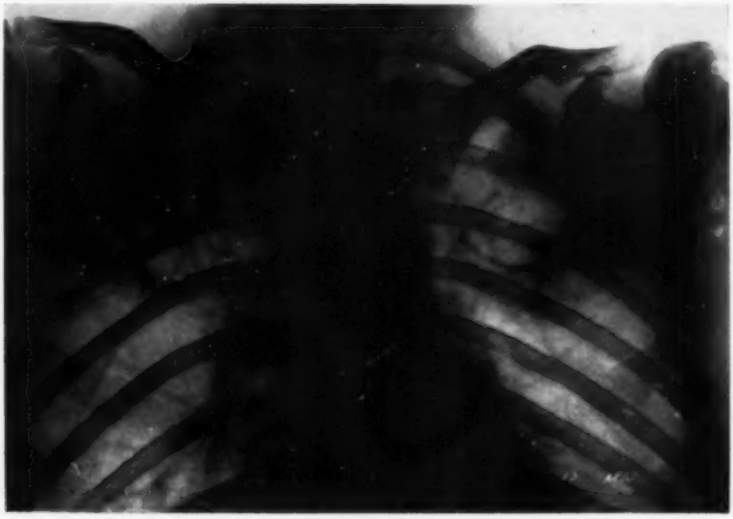

FIGURE 1

promyelocytes 4.5 per cent; myelocytes: neutrophil 22 per cent; acidophil 2.5 per cent; basophil 2.5 per cent; metamyelocytes: neutrophil 7 per cent, acidophil 0.5 per cent, club-forms 15 per cent, subdivided into neutrophil 35 per cent, acidophil 3.5 per cent, basophil 4.5 per cent. A peripheral blood smear showed anizocytosis and a few nuclear red blood cells.

The bone marrow was rich in cells with marked predominance of white cells. Granulocytes were in all stages of development with disturbances in maturation. Red blood cell system, 2 per cent. Basophil erythroblasts 0.5 per cent, polychromatic 1 per cent, acidophil 0.5 per cent. White blood cell system, 95 per cent. Myeloblasts 4 per cent, promyelocytes 6 per cent, myelocytes: neutrophil 25 per cent, acidophil 4 per cent, basophil 1 per cent; metamyelocytes: neutrophil 11 per cent, acidophil 1 per cent, basophil 0.5 per cent; club-forms: neutrophil 7 per cent, acidophil 1 per cent, subdivided into neutrophil 23 per cent, acidophil 3 per cent, basophil 1.5 per cent, multilobular 7 per cent. Lymphatic system: lymphocytes 1 per cent. Reticulo-endothelial system (1.5 per cent): reticular cells proper 0.5 per cent, plasmocytes 1 per cent. Undifferentiated cells, 0.5 per cent. No Koch's bacilli found in the sputum.

X-ray film inspection revealed right apical pleural thickening. Beyond the shadow of the right clavicle a bean-shaped cavity was visible with small surrounding infiltration (Fig. 1). Erythocyte sedimentation rate 55/93.

Diagnosis: chronic myeloid leukemia accompanied by tuberculosis.

Treatment consisted of administration of nitrogen mustard, vitamins, iron and hydrochloric acid, liver extracts, streptomycin and isonicotinic acid hydrazide (isoniazid). After three months, she was discharged on December 19, 1953 with subjective and objective improvement. The liver projected one finger below the right costal arch and the spleen extended to the umbilical line. Leucocytes 15,500 per mm,^{3} including club-forms 2 per cent, subdivided into neutrophils 72 per cent, acidophils 2 per cent, lymphocytes 17 per cent, monocytes 7 per cent. Erythocyte sedimentation rate was 18/34.

In mid-February, 1954, she was again admitted to the in-patient department because of marked debility, a tumor in the abdominal cavity and fever. After some days, she was sent to one of the medical clinics of the Medical Academy, where tuberculosis with infiltrations and destruction of the right pulmonary apex associated with chronic myeloid leukemia was diagnosed, although no Koch's bacilli were found in the

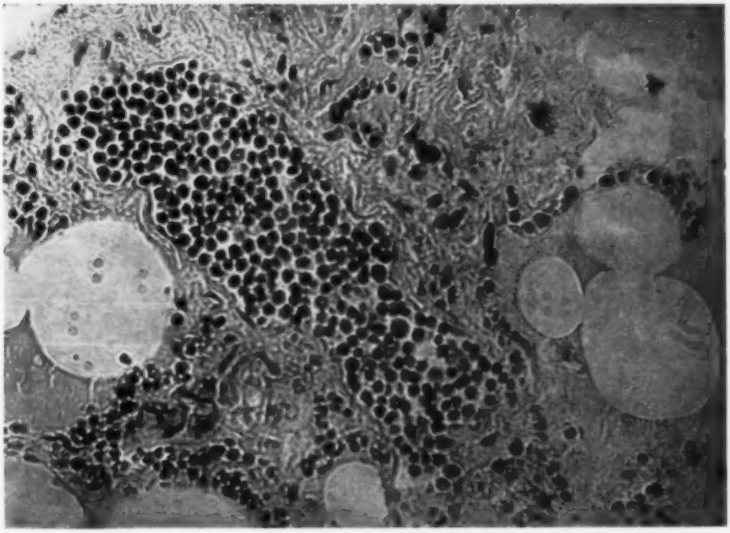

FIGURE 2

sputum. X-ray irradiation of the spleen was applied under a screen of streptomycin and isoniazid. She was discharged from the clinic on June 25, 1954 in an improved condition.

She reported to the in-patient department for the third time August 14, 1954 on account of increasing debility, lack of appetite, subfebrile condition and cough. A few days previously she had an attack of pain in the left lumbar region radiating towards the symphysis pubis. The pains were accompanied by ischuria.

She was again referred to the clinic, where Fowler's fluid vitamins, blood transfusions, streptomycin and isoniazid were applied without any major improvement.

She was sent for the fourth time to our medical department on January 24, 1956 in a grave condition, with pains in the left lumbar region and marked debility. She was cachectic, with dry, weakly elastic and pale skin, disappearance of the subcutaneous fatty tissue, and dry, greyish-white furred tongue. Lymph nodes were not palpable. Lungs: in the right supraclavicular, supraspinal and scapular regions single small râles were heard. In the supraspinal region adjacent to the spine, there was a bronchial respiratory murmur. The percussion notes were normal. There was no cardiac changes. Pulse moderate, pressure normal, 96/min. Arterial pressure 138/80 mm Hg. The lower margin of the liver projected two fingers below the right costal arch, the spleen extended to the symphysis pubis and the crest of the right ilium. Supplementary examinations: Hemoglobin 32 per cent, erythrocytes 1,800,-000, leucocytes 185,200 per mm,^{3} colour index 0.88. Leucocyte count in percentage: myeloblasts 6.2 per cent, promyelocytes 8.1 per cent, myelocytes. The erythrocyte sedimentation rate was 20/40. No Koch's bacilli cent; metamyelocytes: neutrophil 11.1 per cent, acidophil 4.6 per cent, basophil 1.4 per cent, club-forms 22.2 per cent, subdivided into neutrophil 16.4 per cent, acidophil 3.2 per cent, basophil 0.2 per cent; lymphocytes 9.3 per cent, monocytes 1.5 per cent. The peripheral blood smear showed anizocytosis, anizochromia, micro-, macro- and poikilocytes. The erythrocyte sedimentation note was 20/40. No Koch's bacilli found in the sputum. Urine: specific gravity 1010, albumen 0.33 per cent. In the sediment, erythrocytes mostly deformed, 40 — 50 in the field of vision, leucocytes 10 — 15 in the field of vision. Liver function tests were normal. Hijmans van den Bergh reaction was negative. Resistance of erythrocytes to hypotonic solutions of NaCl; beginning of hemolysis 0.5 per cent, complete hemolysis 0.38 per cent. Bilirubin level in the blood serum 0.3 mg per cent. Blood urea level 260 mg per cent. Urography was not performed because of the grave condition of the patient.

At this stage, the patient was examined by the district consultant, who raised doubts as to the correct interpretation of the radiologic picture of the thorax and the diagnosis of the specific process in the lungs.

She died with symptoms of uremia and circulatory failure two weeks after admittance. Post-mortem examination showed marked enlargement of the spleen, leukemic infiltrations in the kidneys, liver, spleen, lymph nodes and striated muscles. Adhesions at the apex of the right lung. In cross-section, there was a cavity the size of a chestnut with ragged walls, surrounded by infiltrated tissue, in the apical portion of the upper lobe

of the right lung, left pyonephrosis caused by stone, pulmonary edema. Histopathologic diagnosis (Department of Morbid Anatomy, Gdansk Medical Academy; Director, Professor W. Czarnocki, M.D.): in sections from the liver, spleen, kidneys, lymph nodes, striated muscles, lungs and sternum was the picture of myeloid leukemia. In the lungs, besides infiltrations in the connective tissue and alveolar walls, leukemic elements were present in the lumina of the dilated capillaries (Fig. 2).

Discussion

The constant absence of tuberculosis bacilli in the sputum in cases of leukemia taking a course with pulmonary changes aroused the suspicion of leukemic infiltrations.

In the course of chronic (but more seldom of acute) lymphatic leukemia, the mediastinal lymph nodes frequently undergo enlargement. In some cases, they give the clinical and radiologic picture of mediastinal tumor. The pressure on the larger bronchi causes atelectasis or emphysema in the corresponding segment of the lung. In the case of pressure on a vein there appear symptoms of stagnation and transudate or a syndrome of the *v. cava superior* in the form of edema of the skin of the face, neck and chest and a stagnant thoracic venous network. The milky effusion into the pleura is explained by the pressure on the thoracic tract and lymphatic vessels.

Falconer and Leonard[5] observed enlargement of the mediastinal nodes with direct infiltration of the pulmonary tissue in 41.7 per cent of cases of chronic lymphatic leukemia; changes in the nodes with infiltrations in the bronchi and peribronchial tissue in 8.3 per cent; changes in the nodes and bronchi with infiltration of the character of lobular pneumonia in 16.6 per cent; changes in the nodes accompanied by infiltrations corresponding to bronchial pneumonia in 16.6 per cent; miliary foci in 16.6 per cent; 64 per cent of cases were complicated by effusion, nearly one-third of which had bilateral effusion.

The syndrome of objective symptoms includes cough, pain and dyspnea. Râles appear in bronchial stenosis or secondary infection.

The physical symptoms depend on the nature and extent of the mediastinal and pulmonary changes.

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Case of Aspergillosis Treated with Amphotericin 'B'

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The problem of pulmonary aspergillosis is not new. The genus of moulds "Aspergillus" was described and named by Micheli in 1729. The name was probably given because of the similarity of the spore-bearing heads, and the brush used for sprinkling holy water (aspergillum).

This fungus was first found to be invasive in 1815 by Mayer, who discovered it in the lungs of a jay, later by others in different birds, and still later, in 1887, in a laryngeal swelling in a horse.

Fungus infection in man was probably first described by Hughes Bennett in 1842 in the *Transactions of the Royal Society of Edinburgh*. The fungus in this case was thought at that time to be a penicillium, but may have been a species of aspergillus. The same year a more or less similar case was described in Germany, and in 1855 a fungus infection was found in a patient who also had cancer of the lung.

The first unquestioned case of human pulmonary aspergillosis was described by Sluyter in 1847 in Berlin, and in 1856 Virchow collected four cases of pulmonary aspergillosis in patients dying of other diseases. Virchow's account (the only one in the history of the disease mentioned in Garrison-Morton) begins, as we still must begin, with the problems of definite diagnosis, and a rather vexed statement of the special problems of mycology.

One might note in passing the preponderance of cases from the European mainland. The best readily available history of the disease is given by Hinson et al in *Thorax*, December 1952.

This fungus can be grown on simple media. Sabouraud's media is often used, but ordinary blood agar is reported to be adequate for primary isolation. Clayton has pointed out recently that fungi may be separated more readily by incubating cultures at both 22 degrees room temperature, and 37 degrees centigrade simultaneously. Penicillium, for example, grows more commonly at 22 degrees, but *aspergillus fumigatus* at 37 degrees. Aspergillus may be incubated at temperatures up to 45 degrees centigrade which may be of further help in differentiating it. If sub-cultures are made on medium containing penicillin and streptomycin, to which aspergillus is resistant, bacterial contamination should be eliminated.

A colony of aspergillus is a white mass of interweaving mycelial threads, from which occasional cells enlarge known as "foot cells." These give off a shoot which elongates upward, and bears a swollen vesicle at its free uppermost extremity. From this vesicle shorter stalks arise like the bristles of a brush *(phialides)*, and on these, in turn, are born the spores *(conidia)*. These may be coloured, giving the different tints to the mature colonies, and assisting in separating the genus into at least four groups, pathogenic to man, of which *aspergillus fumigatus* is much the most common (Figure 1).

The fungus is common in soil and decaying matter (compost piles,

Presented at the Ontario Laennec Society (Toronto)—October 31, 1958, Niagara Peninsula Sanatorium, St. Catherines, Ontario, Canada.

spoiled grain, hay, straw and rotting wood). It is also a common pathogen of birds. These two factors explain the occurrence of the disease among agricultural workers, and those dealing with birds (bird crammers). However, the ubiquity of the spores assures the occurrence of the disease among all groups.

It is improbable that the fungus is always a secondary invader of already diseased tissue such as has been suggested occasionally. A primary form does occur, but it is not as common as the secondary variety. Riddell grew *aspergillus fumigatus* from 55 patients of 1,060 consecutive admissions to Brompton Hospital, twelve of whom were treated for bronchitis, eleven for asthma, seven for pneumonia, two for tuberculosis, four for carcinoma of the lung, two for lung abscess, one for sarcoidosis, three for heart disease, and five for diseases other than pulmonary. The remaining eight cases were treated for aspergillosis, but in at least two of the others listed, mycetomas were present along with the presenting disease.

In order to assess the frequency of fungal infections (whether pathogenic or not) in this area, we cultured sputum for fungi from a more

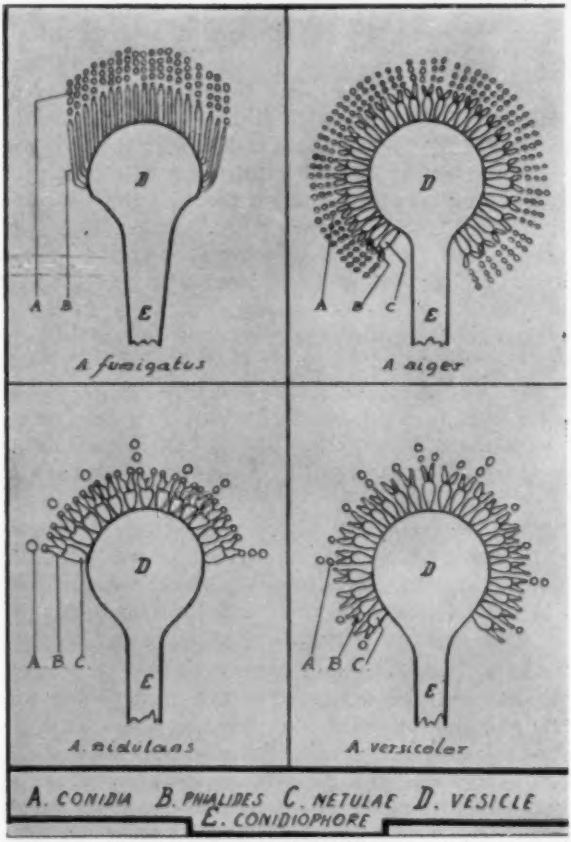

FIGURE 1: Diagram showing morphological differences between strains of fungus *Aspergillus*. Reprinted from THORAX, 7, 317, 1952.

or less random group of older admissions to this sanatorium between March and July, 1959. Seventy cases were examined. In 26, no fungi were found; in 11, candida albicans was found; in 33, aspergilli were found. This indicates either an unexpectedly high incidence of infection with aspergilli, or a peculiar enthusiasm for the fungus in our laboratory. The diagnoses in the 33 patients growing aspergilli were later proven to be tuberculosis (10), asthma, bronchitis and emphysema (9), heart disease (5), bronchogenic carcinoma (3), lung abscess (2), empyema (1), and one whom we strongly suspect was another case of aspergillosis. Two cases were undiagnosed. There did seem to be a slight rise in incidence during the middle period when our weather is quite damp, with perhaps a little less in the colder and warmer periods, though much more work would be needed to prove this. Of those whose sputum grew aspergilli, 14 were skin tested with the antigen, and of these, 8 showed positive reactions. In 2 of these at least, the finding may have been of importance clinically.

The disease may be classified:

1. Acute — resembling bronchopneumonia.
2. Chronic — including mycetomas, resembling fibroid tuberculosis.
3. Allergic — producing bronchospasm and dyspnea ("Farmer's lung").

The case for discussion now came to our attention in the spring of 1950. The patient, at that time a 32-year-old white housewife, was found to have light infiltration in the first and second anterior interspaces on the right, with somewhat heavier infiltration in the same area on the left. No definite cavity was found on tomographs. She was admitted to the Niagara Peninsula Sanatorium on April 3, 1950. At that time, she was asymptomatic, family and occupational history were non-contributory, and physical examination revealed a normally developed fair-haired, blue-eyed, white woman, of approximately stated age, with no abnormality. All her laboratory examinations were within normal limits, although her differential white count showed only 23 per cent lymphocytes (total white count 9,300). One specimen of gastric washing was reported to be positive for tubercle bacilli on culture. She questioned this, but it was impossible to check the finding when her objection was known. All other sputum and gastric specimens were negative on smear and culture for tubercle bacilli.

She was given approximately 36 grams of streptomycin (1.0 gram per day) along with PAS. Right pneumothorax was established followed by pneumonolysis in May and June, 1950, and left pneumothorax was established in July, followed by pneumonolysis on that side in September, 1950. PAS was continued until her discharge on May 3, 1951.

She returned to her home and resumed light housekeeping for her husband and one son. Fluid formed in the right pleural space in early 1952, and the pneumothorax on that side was abandoned in June, 1952. Fluid obtained on aspiration of the space in May 1952 was negative for tubercle bacilli on smear, but positive on culture. Smear at that time showed abundant white blood cells, polymorphonuclears predominating. No non tubercle bacilli were grown. The left pneumothorax was discontinued uneventfully in July, 1956.

In the fall of 1955, she developed what was thought to be a cold abscess on her right anterior chest wall, above and medial to the breast. This was aspirated on several occasions, but no bacteria were found on smear or culture. She was begun on isoniazid (100 mgms. t.i.d.) and PAS (12.0 grams daily) toward the end of 1955, and these were continued until her second admission in the fall of 1957. During a large part of this time, she was in bed at home.

In June, 1956, the abscess disappeared. She was seen by our consultant surgeon at that time. It was agreed that the condition was probably tuberculous and that nothing other than periodic aspiration, along with her antituberculous drugs was indicated.

Nothing further happened until June, 1957 when she developed pain in the region of the old abscess and the mass re-appeared. She was re-

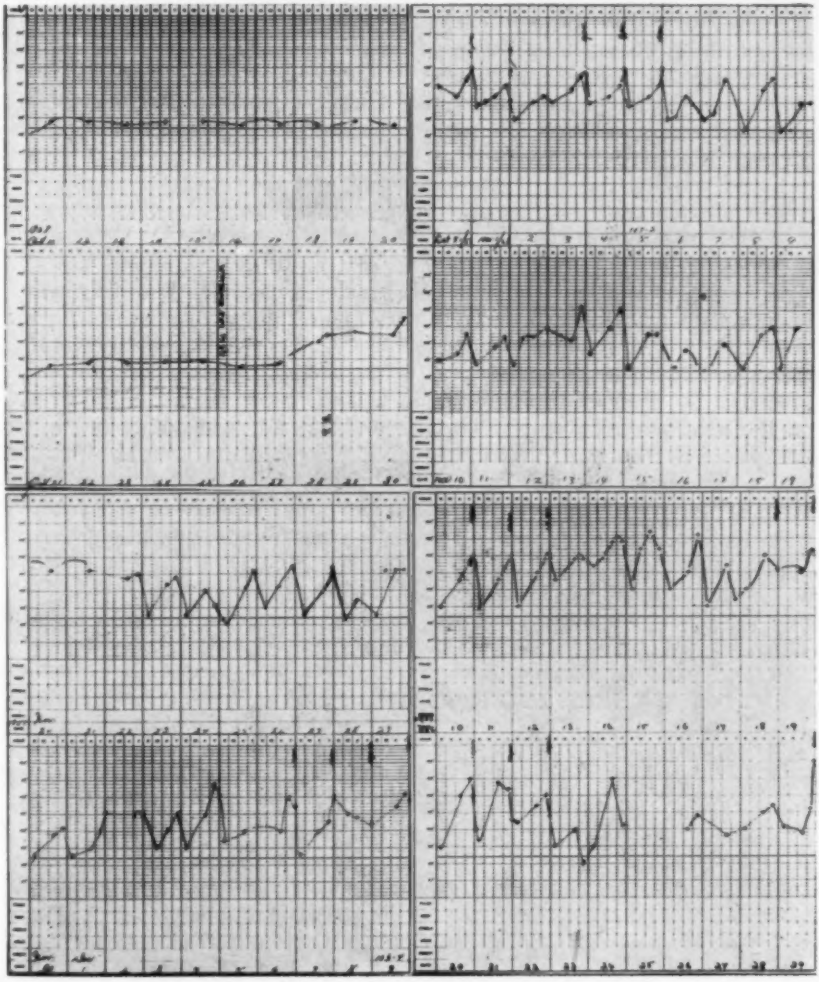

FIGURE 2: Temperature charts October 11 to December 29, 1957.

admitted on September 21, 1957, and shortly after this admission, in spite of repeated aspiration, the abscess discharged spontaneously, close to the lateral border of the sternum, leaving a chronic sinus about 0.5 cms. in diameter, with slightly overhanging edges. All material cultured from the abscess and sinus was negative on smear and culture for all bacteria.

Chest films on this admission showed an appreciable amount of disease in both lungs, with some suggestion of excavation on the left side.

Following this admission, many (70) specimens of sputum were all negative on smear and culture for tubercle bacilli. Other laboratory data were within normal limits, except that out of a total white count of 10,100, only 7 per cent were lymphocytes. Sedimentation rate was 11 mms. per hour (Westergren).

She had no symptom referable to her respiratory or other systems on admission, and there was no abnormality on physical examination, except diminution of breath sounds (which we associated with the former pleural reaction) on the right side.

She was begun on antituberculosis drugs on September 24, 1957, using streptomycin and PAS alternating month with isoniazid and pyrazinamide.

There was nothing further remarkable, and she continued to feel well (even if somewhat restless and apprehensive) until the day following her first injection of 0.5 c.c. of Asian influenza vaccine on October 26, 1957. At that time, this vaccine was offered to all the patients, and a great many accepted it (in two doses of 0.5 c.c. each) without any symptoms whatever. On October 27, she had malaise and headache, and the following day her temperature rose to 104° degrees F. in the evening. Fever continued each day thereafter for several months (Figure 2). It was usually between 99 and 100° in the morning, rising to 101 or 102 in the afternoon. In spite of this fever, she had remarkably few other symptoms at first, apart from fatigue. Her appetite and weight remained about the same. She had no cough or chest symptoms until the beginning of her fever, when an unproductive cough appeared. After about a week this became productive of dark greenish sputum, about two to three ounces in volume early in December, increasing further to three to four sputum boxes of foul greenish brown sputum by the first of February. This sputum was sufficiently thin to run out of the patient's mouth, when she was turned on her side.

In spite of her illness, the discharge from the sinus in the anterior chest wall decreased, and finally stopped, with healing of the sinus. Roentgenograms failed to show involvement of ribs or sternum. Chest roentgenograms at the beginning of her fever showed no significant change. However, by the end of January, 1958, chest films (including tomographs) showed extensive cavitation in the right upper lung field (Figure 3).

Sputum continued to be negative for tubercle bacilli. Only the common inhabitants of the respiratory tract, including non-haemolytic streptococci and staphylococci and pyocyaneus could be cultured. These were reported at various times to be sensitive to tetracycline, streptomycin, erythromycin, chlortetracycline, and all these were used in the usual doses without any benefit whatever.

A biopsy of the sinus tract was taken. This showed caseous granulomatous inflammation compatible with a diagnosis of tuberculosis, but no acid-fast bacilli or fungi could be identified.

There was a small collection of fluid lying over the apex of the left lung. In an attempt to obtain further material for culture, this was aspirated, but only a few c.c.'s of brownish fluid could be obtained, and this was sterile on culture. Unfortunately, following this aspiration she developed a small tension pneumothorax, which persisted for some months gradually decreasing in size.

Spinal tap was done, and cerebrospinal fluid obtained showed only a few white cells. It too was sterile on culture.

Early in January, 1958, we obtained a culture of *aspergillus fumigatus*. This was confirmed by the laboratory of the Mountain Sanatorium, and the Laboratory of the Provincial Department of Health in Toronto. We continued to obtain copious growth of this fungus on each occasion when her sputum was cultured until after specific therapy had been begun in February. When this fungus was first reported, we were not convinced it was the cause of her illness.

Examination of her blood showed a falling haemoglobin, which fell even further on treatment (down to 42 per cent by the middle of February, 1958), with a corresponding fall in red blood cells to 2,760,000 at the same time. Her white blood count rose to 15,400 by the end of December, 1957, and then fell somewhat for the next month to about 12,500. During treatment in February, it fell to 5,600 by the middle of the month, and then remained at about seven to eight thousand. She continued to show a low lymphocytic count ranging from 4 per cent to 12 per cent (usually about 6 or 7 per cent) of the total count. At no time did she have remarkable eosinophilia. In November, 1957, her eosinophile count was recorded once early in the month as 7 per cent, and late in the month as 9 per cent, but it varied principally between 1 and 3 per cent. Monocytes did not rise above 6 per cent. Her sedimentation rate rose to 84 mms. per hour (Westergren) by the end of January, 1958, but then

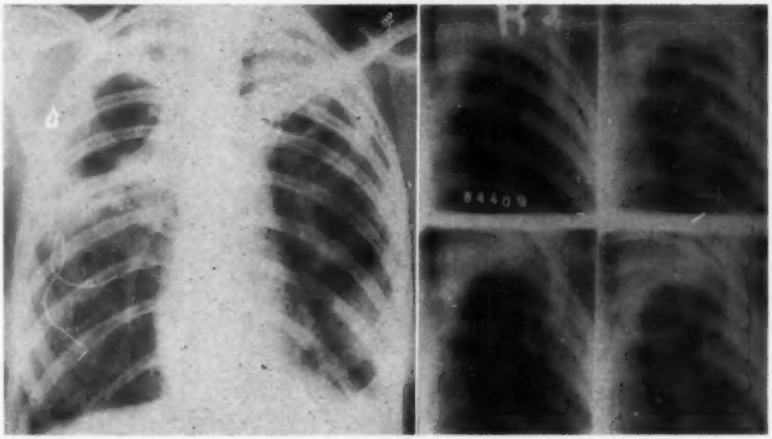

FIGURE 3: Chest roentgenogram (and tomograph films at 4, 5, 6 and 7 cm levels from the posterior chest wall) January 28, 1958.

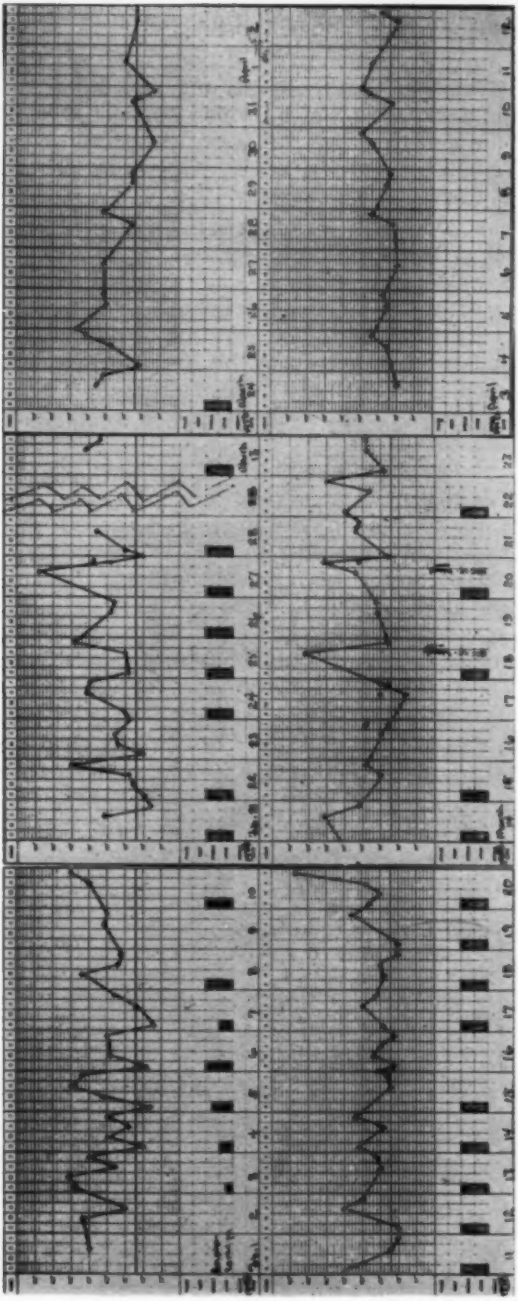

FIGURE 4: Temperature chart and record of Amphotericin administration February 1 to April 12, 1958.

gradually fell on specific therapy, and was recorded at 10 mm/hr. in June, 1958.

Electrophoretic fractionation of her serum in January, 1958 showed very low albumin with high alpha, increased beta and high gamma fractions.

When specific therapy was begun in February, she was gravely ill and weighed 94 lbs.

On February 3, 1958, amphotericin-B (Fungizone-Squibb) was begun. It was suggested that the dose be gradually increased to the maximum tolerated, but not to exceed 1.5 mgm. per kilogram of body weight. On the first day, 12.5 mgms. were given intravenously over a period of six hours. She developed some rigor and nausea, but on the following day 25 mgms. were given; the next day 37.5 mgms., and by the fourth day a full dose of 50 mgms. was used. The severity of the rigor and nausea on that day induced us to decrease the dose to 25 mgms. on the fifth day, but on the sixth we resumed the 50 mgm. dose, and this was continued daily (except Sundays), in spite of fevers, nausea and headaches till the middle of March (Figure 4).

During this time, cultures of her sputum for *aspergillus fumigatus* produced the following record:

January 29: 3 plus growth
February 4: 4 plus
February 6: slight
February 8: 3 plus
February 10: slight
February 11: 3 plus
February 12: 1 plus
February 14: 3 plus
February 17: slight
February 18: slight

All subsequent cultures have shown no fungi up to the present.

The amount of cough and sputum decreased steadily, and the sputum became clear.

The most difficult problem, other than the toxic reaction during this period of amphotericin administration was the preservation of adequate venous channels for the introducing of the drug. A small amount of heparin was added to each bottle of solution in an attempt to solve this problem.

Because of the low haemoglobin in the middle of March, two transfusions of blood were given and the frequency of administration of amphotericin was decreased. On March 22, a small amount of the solution went interstitially. Following this, she had a little increase in expiratory effort, but she did not complain of dyspnea. On March 24, a larger amount of amphotericin escaped into the tissues. After this, she became severely dyspnoeic for several days. This was treated with aminophylline, steroids, and isuprel aerosol, and she gradually improved. The tissue at the site sloughed, and healed slowly. No further amphotericin was given.

After the discontinuance of therapy her fever gradually disappeared, and her general condition improved tremendously. She was allowed

outside walking exercise in June, and was discharged on July 12, 1958. Although her activity is still limited, her condition has remained satisfactory. Chest x-ray films show less excavation on the right.

In spite of the extensive pulmonary involvement, she has no dyspnoea on ordinary activity. However, ventilation studies in May, 1958 showed a total vital capacity of 1.25 litres (44 per cent of predicted normal), and a 3-second vital capacity of 39 per cent of predicted normal.

We feel that this is a case of aspergillosis complicating pulmonary tuberculosis. The relation of the influenza vaccine to the onset of clinical aspergillosis is a mystery. She states that she could never eat chicken without a gastro-intestinal upset and we understand that the vaccine is produced in eggs. Whether some allergic phenomenon lowered her resistance sufficiently to permit invasion by the fungus is a matter of conjecture.

There can be no reasonable doubt that, however severe the reactions to the amphotericin may have been, the drug was life-saving to this patient.

ACKNOWLEDGMENT: We should like to acknowledge gratefully the assistance of the E. R. Squibb Co., and its medical directors in supplying the Amphotericin-B.

We also wish to thank Mr. Ronald Phythian, Mrs. Martha Albon, and Mr. Guido Senitza for the cheerful and efficient way in which the laboratory handled the considerable extra burden.

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Editorial

THE WESTERN WORLD AND THE WORLD OF PEACE

The basic theme of this editorial is a Western physician's reply to the laudable and timely medical philosophy now emerging from the ancient wisdom of India. Western medicine is a limited contribution of our industrial civilization in the mid-20th century; however, it has evoked a reappraisal of older concepts that are now slowly evolving biologically as the dominant factor in present therapy.

To obtain the proper perspective it is necessary for American medicine to disentangle itself momentarily from the technological impact that followed the industrial revolution in the mid-18th century. This revolution has had international consequences of infinitely greater magnitude than the Western physician realizes. In our laudable effort to cure infectious diseases with antibiotics we unknowingly induced resistant strains or mutations to emerge genetically and these lethal species are now being biologically perpetuated about the world.

With the expanding clinical use of penicillin during World War II, bacterial geneticists at that time showed the medical profession the urgent need to understand basic laws of microbial behavior or bacterial ecology in treating infectious diseases in man. They warned that unless the advice was heeded clinically and appropriate combinations of antibiotics—preferably with detergent solvents—were used, resistant strains would emerge and perpetuate bacterial species ultimately detrimental to man's welfare. Unfortunately this advice was ignored and as predicted, resistant strains have fundamentally altered the practice of medicine.

If we in the West are to develop medicine benevolently as our greatest remaining asset for a "world of peace," (R. Viswanathan)* our present concepts must be critically reappraised, since they represent historically and clinically the limited medical technological experience of the past two centuries. In order to grasp this opportunity, we must think of our present changing Western technological civilization in terms of the preceding microbiologic epoch of over five billion years. Our greatest obstacle to peace now is the man-made bacterial and atomic mutants. In the daily practice of medicine we produce countless irreversible forms of lethal microbial life, definitely detrimental to man's well-being, not knowing the magnitude of disease that will follow in the wake of these pathogens in the present and future generations. In medicine, microbial evolution should be the matrix of a dedicated spiritual philosophy for man's welfare, ultimately germinating the substance to bring about a world of peace which will be neither East nor West but a blending of our Western technological civilization with the ancient "contemplative aesthetic component" of the East (Raman Viswanathan).

With the inevitable medical resurgence of microbial evolution in the 20th century, we are in essence only updating therapeutically the medical biological knowledge of over a century ago, with however, this great difference: we live in an anxious, atomic world groping desperately for peace. We in the Western world are free now to advance this medical

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"A World of Peace," by Raman Viswanathan, M.D., F.C.C.P.—Regent for India, New Delhi, India. Editorial from DISEASES OF THE CHEST, Official Publication of the American College of Chest Physicians, September, 1958.

philosophy without fear of being ostrasized or persecuted, an ordeal our medical predecessors in the late 18th and early 19th centuries had to accept.

It is of interest to the historian and the physician to observe that in India this new medical world philosophy, which is in essence the cultural distillate of nearly 30 earlier civilizations, has been developed in less than a decade. France, Holland, the Philippines, and more recently Poland, are also in advance of our own country in this clinical integration for treating infectious diseases.

Since 1955 this recent Indo-American philosophic contribution for peace presented in Dr. R. Viswanathan's editorial has been integrated surgically with the clinical concepts of our Western geneticists by Dr. R. N. Mitra in Calcutta and in the non-surgical treatment of extensive suppuration of the lung by Bindra Ban in New Delhi since 1950. Their results with multiple chemotherapy confirm our own since 1945, emphasizing that combinations of appropriate antibiotics can cure many previously incurable infectious diseases, including tuberculosis, often without any surgery or hospitalization. With our present medical knowledge coordinated one hopes that a more rapidly expanding and realistic genetic approach will dominate future Indo-American medical efforts for international peace.

For the first time man may now use his new biomedical conceptual tools in an East-West medical synthesis to help bring about one world of peace. In Western man's evolution he has now attained a spiritual and materialistic superiority which enables him to perpetuate this medical advantage. Some institutions of learning, however, still lag biologically to the detriment of the medical world.

In Geneva, one month before the international meeting to advance the "Atoms for Peace" program, a paper was presented by a physician (E.J.G.), urging an appraisal of these medical principals in the use of genes for peace, and showing clinically that many previously incurable diseases which have afflicted man during all recorded history could be cured by this new medical approach. The director of the seminar was another Indian, V. G. Vaishanpayan, of the N. W. Wadia Charitable Hospital in Sholapur, India. "Atomic Medicine," with its connotation so tragically synonymous with war, will be short-lived unless the atomic physicists shift to a major interest in microbiological research as some of the original investigators have done. This simple medico-genetic contribution will do more to help the sick and feed the hungry than "atoms for peace."

Never in its history has American medicine been in a more advantageous position to help solve an acute international health problem. There is unanimity of opinion in world politics that medicine should be advanced for peaceful purposes and this biologic and philosophic plea of physicians in the mid-20th century might very well result in a fulfillment of the prophesy of Isaiah: "They shall beat their swords into plowshares, and their spears into pruninghooks: nation shall not lift up a sword against nation, neither shall they learn war any more."

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The President's Page

THE SIXTH INTERNATIONAL CONGRESS ON DISEASES OF THE CHEST

All members of the College know about the coming international congress in Vienna; not all realize that the design of this meeting will qualify it as one of the outstanding events in medical history. Sponsored by the American College of Chest Physicians and implemented by two years of planning and with the know-how acquired by the previous five successful international meetings, the plans have been made to make this one which will long be remembered.

The Council on International Affairs of the College, with our skillful and beloved Past-President, Andrew Banyai, in command, laid the foundation. The Scientific Program Committee of the Congress has designed the structure. The officers of the Congress assisted by many members of the College will complete the program. The material to be presented could not be duplicated in a hundred journals.

The general plan is to present the formal program in four languages (English, French, German and Spanish) simultaneously by tape recordings and expert interpreters. The program will include formal lectures, panel discussions, fireside conferences, colloquia, clinical-pathological conferences and motion pictures on pertinent scientific subjects. We will have the opportunity to meet and hear the masters in their respective fields and to test our own concepts against the backdrop of international opinion.

The formal lecture, while brief, is a source of rich benefit in fact and theory. Here is the kernel of the nut, the gist of the matter.

The panel discussion is a less formal elaboration of a subject presented by experts with possibly divergent views or exact views on specialized segments of a problem. Here there may be an opportunity to make inquiry by a limited number of questions designed to clarify or extend the discussion into channels of particular interest to ourselves.

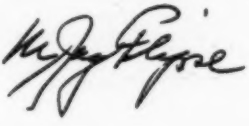
The fireside conferences are a "trade mark" of the American College of Chest Physicians, and are familiar to all of you. These conferences have been so successful that they have been imitated by other medical organizations which is the most subtle form of flattery.

At our international congress, there will be a wealth of topics concerning various aspects of diseases of the chest. Each group will have expert discussion leaders who will be able to surmount the language barrier and bring home to us the various opinions of world leaders on any selected topic. Here we can all join in and become acquainted with experts from other lands whose names have heretofore been our only knowledge of their work. Subjects of discussion will include diseases of the lungs, cardiovascular system and other organs in the chest. There will be experts to discuss angiocardiography, pneumoangiography, cardiorespiratory function and dynamics, postoperative respiratory problems, inhalation therapy, air pollution and many other topics. Here we will have open discussions in an atmosphere of easy companionship.

The colloquia are somewhat new in concept. A small group of experts will exchange ideas on current subjects of research in an attempt to develop new and fertile ideas for further study on research.

The clinical-pathological conferences are always of interest as are the motion pictures from which we learn so easily by visual method.

There is one fact that needs emphasis only for those who have never attended an international congress when doctors, teachers, students and sometimes representatives of the government of the host country, meet to discuss scientific matters pertaining to the cure of some of the diseases of mankind. There inevitably develops a mutual respect and understanding which transcends differences in creed, color, religion and political ideology. This is a most potent contribution to the welfare of mankind and to the universal desire for world peace.



26th ANNUAL MEETING

The 26th Annual Meeting of the College was held at the Saxony Hotel, Miami Beach, Florida, June 8 through 12. More than 1300 members and guests attended the meeting at which one of the finest scientific programs of the College was presented. There was an excellent display of forty-two technical exhibits which attracted a great deal of interest throughout the meeting.

On Saturday night, June 11, the annual Convocation was held and Fellowship Certificates were awarded to 170 physicians. The cocktail party and Annual Presidents' Banquet followed the Convocation. Dr. Seymour M. Farber, President of the College, presided at the banquet and introduced the officials and special guests.

The first prize winner of the College Essay Contest, Mr. D. Jackson Coleman of the University of Buffalo, New York, flew to Miami Beach to receive his certificate and check in the amount of $500.00 and returned to Buffalo immediately following the banquet to be graduated from the University the next day. Dr. James C. Nash, chairman of the Committee on College Essay, made the presentation.

A special certificate was awarded to 14-year old Claremont Carter of Miami for the heart-lung machine which he built, and which was exhibited at the meeting.

Left to right: Claremont Carter, Miami, Dr. Charles P. Bailey and Dr. Arthur M. Master, New York City, viewing Mr. Carter's heart-lung machine.

Dr. Paul H. Holinger, chairman of the Committee on Motion Pictures, presented the annual College film awards. The First Prize Certificate went to Drs. Michael E. DeBakey and George C. Morris, Jr. of Baylor University, for their film "Fusiform Aneurysm of Aortic Arch, Resection and Replacement with Dacron Graft." Dr. Morris was present to receive the certificates. A special certificate was awarded to the U. S. Air Force for its film "Air Travel and the Cardiopulmonary Patient." Major General Oliver K. Niess, Surgeon General of the Air Force, and Lt. Colonel Robert B. Stonehill, Technical Advisor for the film, were present to receive certificates. Dr. Holinger presented certificates of honorable mention to Dr. Chuzo Nagaishi, Kyoto University, Kyoto, Japan, and to Dr. Theodore H. Noehren, University of Buffalo, New York, for their excellent motion pictures "Direct Intracavitary Insufflation with Chemotherapeutic Agent Using Metra's Catheter Via Tracheo-Bronchial Route" and "Intermittent Positive Pressuure Breathing (IPPB/I)—Its Clinical Applications and Administration" respectively.

The 1960 College medal for meritorious achievement in the specialty of diseases of the chest was awarded to Dr. Arthur M. Master of New York City. (See June, 1960 issue of *Diseases of the Chest*.)

Dr. Donald R. MacKay, immediate Past-President, presented the Presidential Scroll to Dr. Farber and the Past-President's pin to Mrs. Farber. The new College President, Dr. M. Jay Flipse of Miami, was then introduced. Mrs. Flipse and Mrs. Alexander Libow received bouquets of red roses as chairmen of the Ladies Reception Committee.

Dr. Farber expressed the appreciation of the officers and members of the College to Drs. Thomas W. Mattingly, Washington, D. C. and R. Drew Miller, Rochester, Minnesota, co-chairmen of the Committee on Scientific Program, and the members of their committee, for the organization of a splendid program; to Dr. Paul H. Holinger, Chicago, and the members of his Committee on Motion Pictures for the excellent film program; to Drs. M. Eugene Flipse, Miami, E. Sterling Nichol, Miami and Jack Reiss, Coral Gables, for the preparation of the extremely well received postgraduate seminars; and to Drs. M. Jay Flipse, Honorary Chairman and Alexander Libow, Chairman of the Committee on General Arrangements and the members of the Florida Chapter of the College for their cooperation in making the annual meeting so successful.

Ladies Activities

The Ladies Reception Committee, under the chairmanship of Mrs. Alexander Libow, planned an attractive program of activities for the ladies. The ladies had a buffet dinner on Friday evening, June 10, at the Delano Hotel, and a brunch at the Fontainebleau Hotel on Sunday, June 12, when a fashion show was presented by courtesy of Burdine's Department Store, Miami Beach. The ladies of the College also attended the Convocation, cocktail party and Annual President's Banquet on Saturday, June 11. Mrs. M. Jay Flipse and Mrs. Seymour M. Farber served as Honorary Chairmen of the Ladies Reception Committee.

Administrative Meetings

The Executive Council, Board of Regents and Board of Governors held their annual meetings in Miami Beach and matters of policy, as well as reports of the College councils and committees were discussed. The proceedings of these meetings and reports of councils and committees will be published in subsequent issues of *Diseases of the Chest*. All of the councils and committees of the College held their annual meetings on Thursday, June 9.

Reports of the President, Treasurer, Historian, Executive Director and the chairman of the Committee on Nominations were presented at the Open Administrative Session on Thursday, June 9. The following officers for the year 1960-61 were elected:

OFFICERS

President-Elect	Hollis E. Johnson, Nashville, Tennessee
First Vice-President	John F. Briggs, St. Paul, Minnesota
Second Vice-President	Charles K. Petter, Waukegan, Illinois
Treasurer	Albert H. Andrews, Illinois
Assistant Treasurer	William E. Adams, Chicago, Illinois
Historian	Carl C. Aven, Atlanta, Georgia

REGENTS

District No. 3	Ross K. Childerhose, Harrisburg, Pennsylvania
District No. 7	Otto L. Bettag, Chicago, Illinois
District No. 9	David H. Waterman, Knoxville, Tennesee
District No. 11	Carl H. Gellenthien, Valmora, New Mexico
District No. 12	George R. Herrmann, Galveston, Texas
District No. 15	Jaime F. Pou, Hato Rey, Puerto Rico

GOVERNORS

Alabama	Paul W. Auston, Langdale
California	Buford H. Wardrip, San Jose
Connecticut	Arnold B. Rilance, New Haven
Georgia	Curtis H. Carter, Augusta
Illinois	Darrell H. Trumpe, Springfield
Louisiana	Lawrence H. Strug, New Orleans
Michigan	Winthrop N. Davey, Ann Arbor
Minnesota	Sumner S. Cohen, Oak Terrace
Mississippi	Robert E. Schwartz, Hattiesburg
Missouri	Charles A. Brasher, Mt. Vernon
New Jersey	A. Albert Carabelli, Trenton
New York	Coleman R. Rabin, New York City
Puerto Rico	E. Martinez Rivera, Hato Rey
Tennessee	Duane Carr, Memphis
Utah	William R. Rumel, Salt Lake City
Vermont	Burton S. Tabakin, Burlington
Wyoming	Francis A. Barrett, Jr., Cheyenne

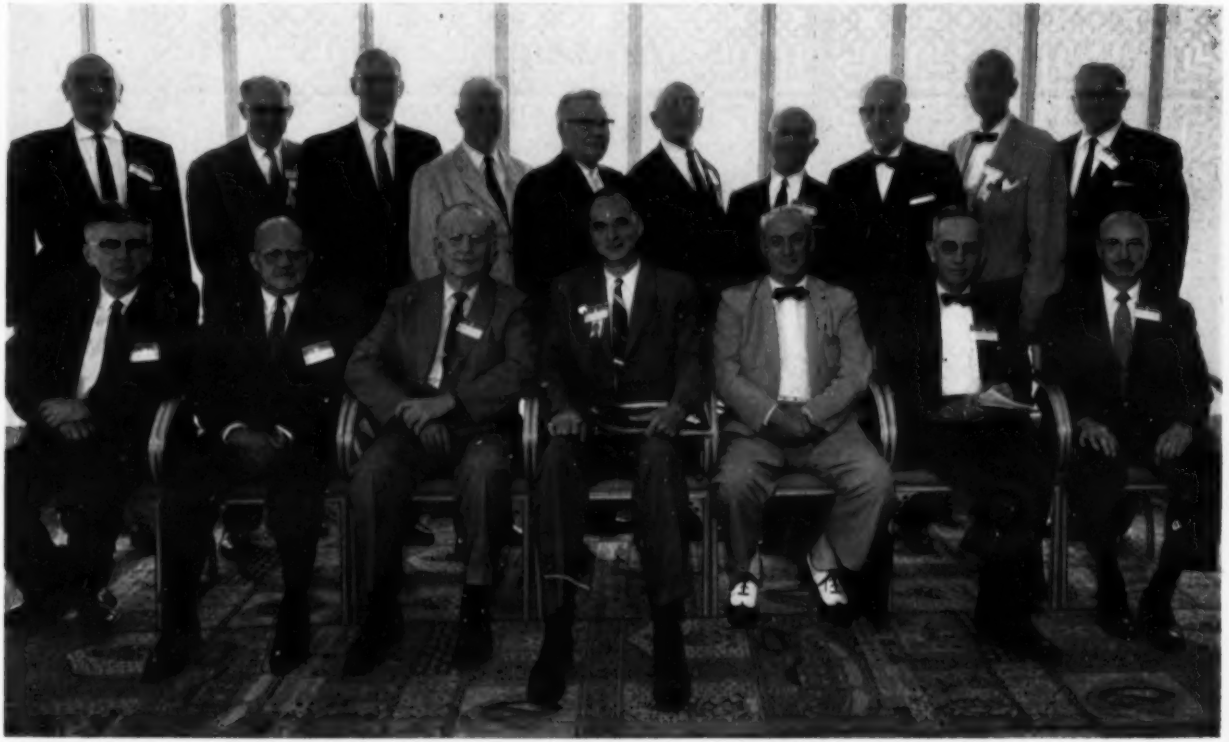
Canada

Manitoba	Lawrence R. Coke, Winnipeg
Saskatchewan	Angus R. McPherson, Saskatoon
Alberta	Leslie McR. Mullen, Calgary

Government Service

Veterans Administration	Edward Dunner, Washington, D. C.

EXECUTIVE COUNCIL, AMERICAN COLLEGE OF CHEST PHYSICIANS



Members of the Executive Council photographed at the annual meeting in Miami Beach. Seated, left to right: Drs. Arthur M. Olsen, Charles K. Petter, John F. Briggs, Seymour M. Farber, M. Jay Flipse, Hollis E. Johnson, Albert H. Andrews. Standing, left to right: Drs. Irving Willner, J. Arthur Myers, Herman J. Moersch, Burgess L. Gordon, Donald R. McKay, Joseph C. Placak, Andrew L. Banyai, J. Winthrop Peabody, Richard H. Overholt and Alfred Goldman.

Latin-American Chapters Celebrate Silver Anniversary of the College

To commemorate the 25th anniversary of the founding of the American College of Chest Physicians, chapters of the College in Central and South America arranged a series of meetings in nine countries to honor Murray Kornfeld, the founder and Executive Director of the College.

PANAMA

The first of these meetings was held in Panama on February 19, 1960, sponsored by the Panama Chapter; Maximo Carrizo, Regent; Rodolfo V. Young, Governor; Alberto Calvo, President; Octovio C. Ferrari, Jr., Vice-President, and Antoine Raymondo, Secretary-Treasurer.

COLOMBIA

On February 20, a meeting was held at the University of Cali, Colombia, sponsored by the Colombia Chapter of the College; Carlos Arboleda Diaz, Bogota, Regent; Rafael J. Mejia, Medellin; Ramon Hernandez, Cali, and Sigfrido Demner, Bogota, Governors. At the meeting in Cali, it was agreed that Colombia should have three chapters, one for Bogota, the second in Medellin and the third chapter in Cali. Plans were effected to organize these three chapters. Guillermo Orozco was elected President of the newly-formed chapter in Cali and Alfonso Mejia Calad was elected President of the chapter in Medellin.

ECUADOR

In Guayaquil, Ecuador, a series of meetings was arranged on February 22 and 23 by Jorge A. Higgins, Governor; Juan Tanca Marengo, Regent of the College, and J. Gonzalo Freile, President of "La Sociedad Ecuatoriana de Tisiologia y Enfermedades del Torax," to discuss the organization of a College chapter in Ecuador.

PERU

On February 24 and 25, meetings were organized by the Peruvian Chapter; Ovidio Garcia-Rosell, Regent; Mario Pastor, President; Marino Molina, Vice-President; Alejandro A. Castro, Secretary; Jose Marie Almandos Velis, Treasurer, and Leopoldo Molinari, Past-President.

CHILE

The next meeting on the west coast of South America was held in Santiago, Chile, on March 10; Hector Orrego Puelma, Regent; Gilberto V. Zamorano, Valparaiso; Ildefonso Garreton Unda, Concepcion, Governors. In Chile, it was also recommended that three chapters be organized, with headquarters in Santiago, Valparaiso and Concepcion. During the visit of Mr. and Mrs. Murray Kornfeld to Santiago, they were invited by Dwight D. Eisenhower, President of the United States of America, to attend an official reception given in honor of the President of Chile, the Honorable Jorge Alessandri.

ARGENTINA

Meetings on the east coast of South America were held in Buenos Aires on March 16, and Cordoba, Argentina, on March 18; Raul Vaccarezza, Buenos Aires, Regent; Manuel Albertal, Buenos Aires; Agustin Caeiro, Cordoba, and Justo Lopez Bonilla, Rosario, Governors. The organization of these meetings was also due to the efforts of Carlos Walter Grobli, President; Jose Maria Leston, Vice-President; Fernando del Valle, Secretary-Treasurer, all of Buenos Aires, and Alberto Chattas and Isaac Wolaj of Cordoba. It was with regret that we learned of the passing of Doctor Grobli in June of this year.

In Cordoba, Mr. and Mrs. Kornfeld placed a wreath on the grave of Professor Gumersindo Sayago, the former Regent of the College in Argentina, at a special dedication service.

URUGUAY

On March 22, a meeting was arranged by the Uruguay Chapter of the College; Fernando Gomez, Regent; Armando Sarno, Governor; Juan E. Alejandro Victorica, President, and Rene Racine, Secretary-Treasurer.

BRAZIL

Meetings of the following College chapters were held in Brazil: Sao Paulo, March 24; Euryclides Zerbini, Governor; Alberto Chapchap, President; B. J. Fleury de Oliveira, Vice-President, and Alberto Adde, Secretary-Treasurer. Joao Bettega, Governor of the College in Parana, also attended the meeting in Sao Paulo. Two meetings by the Rio de Janeiro Chapter; Manoel de Abreu, Honorary Regent; Aloysio de Paula, Regent for South Brazil; Mauricio Teichholz, Governor; Edmundo Blundi, President; A. Burlamaqui Benchimol, Vice-President, and Jose Carvalho Ferreira, Secretary-Treasurer. The second meeting in Rio de Janeiro was arranged by Antonio Ibiapina and Newton Bethlem. The most recently organized chapter in the state of Rio held a meeting in Niteroi on March 30; Antonio Abunahman, Governor; Carlos da Silva, President; Nelson Douat, Vice-President; Gil Alves Lima, Secretary, and Plinio Jotta Tantarino, Treasurer.

Meeting sponsored by the Peruvian Chapter, February 25, 1960, in honor of Mr. and Mrs. Murray Kornfeld.

On April 1 and 2, the Bahia Chapter arranged a series of meetings; Jose Silveira, Regent in North Brazil; Manoel Ezequiel, Governor; Adelaido Ribeiro, President, and Itazil dos Santos, Secretary-Treasurer. Mr. Kornfeld was presented with a certificate of Honorary Membership in the Instituto Brazileiro para Investigacao da Tuberculose (IBIT) at a special ceremony arranged for this purpose and attended by many of the officials of the College and other dignitaries. Epilogo de Campos, Governor in Belem, was also present at these ceremonies. It should be noted that Honorary Membership in the Brazilian Tuberculosis Society was conferred upon Dr. Donald R. McKay, Buffalo, New York and Dr. Seymour M. Farber, San Francisco, California. Certificates were presented to them by Mauricio Teichholz, Governor of the College for Rio de Janeiro.

VENEZUELA

A traditional breakfast was held in Caracas attended by most of the members of the College in Venezuela. This was followed by a meeting of the Venezuelan Chapter on April 7; Pedro Iturbe, Maracaibo, and Julio Criollo Rivas, Caracas, Governors; Humberto Delgado Rivas, Maracaibo, President; Carlos Ortega, Valencia, Vice-President, and Alejandro Principe, Caracas, Secretary-Treasurer. A complete report of the meetings held in Central and South America was given to me by Mr. Kornfeld and will be presented at the Administrative Session of the Congress in Vienna, August 28, 1960.

While in Salvador, Bahia, arrangements were completed for the participation of the Council on Pan-American Affairs of the College in the meeting of the Union of Latin-American Tuberculosis Societies (ULAST) which was held there July 10-14, 1960, under the direction of Doctor Jose Silveira, President of this Congress.

SUMMARY

In all of the countries visited by Mr. Kornfeld, arrangements were made for the participation of members of the College in the 25 international committees, which will meet in Vienna on Saturday, August 27. The exchange of Fellows among the various countries where there are College members was also discussed with officials of the College in these countries. It is expected that there will be greater participation by students in the medical schools in the Latin-American countries in the Essay Contest which is conducted each year by the Council on Undergraduate Medical Education of the College. Cash prizes totaling $1000 are awarded to the winners in this contest.

A number of books sponsored by the College have been translated into Spanish and these books are enjoying popularity in the Latin-American countries. There is also a demand for the motion picture services in films dealing with chest diseases and approved by the Committee on Motion Pictures of the College. Many of these films will be shown at the meetings of the College chapters throughout Central and South America. A number of the chapters have indicated that they are planning to organize Fireside Conferences in order to stimulate the informal exchange of ideas among all of the members of the chapters.

The above activities of the College were discussed by Mr. Kornfeld at 16 meetings organized by the chapters in Central and South America. Mr. Kornfeld reported that the first 25 years have been devoted to the building of the College structure, and that the chapters must now take the lead in developing effective programs to promote the recent advances in the speciality of chest disease. The international committees, on which 940 members from 67 countries are serving, will meet every two years at the time of the international congresses of the College, and they will play an important part in furthering the objective of the society. The more than 7000 members of the College, situated in 89 countries and territories throughout the world, will benefit as a result of the deliberations of the activities of the international committees.

Social affairs were arranged in each country to honor Mr. and Mrs. Murray Kornfeld in the commemoration of the Silver Anniversary of the College. Many of the College members in Central and South America plan to attend the Congress in Vienna this year.

Jose Ignacio Baldo, M.D., Chairman,
Council on Pan-American Affairs,
American College of Chest Physicians.

President's Address

THESE CHANGING TIMES

M. JAY FLIPSE, M. D.
Miami, Florida

It has, for many years, been the habit in the American College of Chest Physicians to permit the incoming President to address the neophytes who are gathered at the annual convention for their official induction. In this capacity, and as the present spokesman of the College, I salute you, and welcome you to fellowship in a unique organization. You are now affiliated with the most rapidly growing and largest self-sustaining international medical organization in the world. Its membership embraces the various disciplines of medicine, surgery, pathology, epidemiology, public health, radiology and research, as it pertains to diseases of the heart and lungs. Its members number more than 7,000 and are representative of the best medical skill in the United States and 89 other countries and territories. Among the members of the College are the most eminent men of medicine of this century. Indeed the Silver Anniversary Membership Roster published last year, reads like a medical "Who's Who" of the world. It can truly be said that "The sun never sets on the membership of the American College of Chest Physicians."

I am highly honored in addressing you, for among your group there will be famous men of the next century whose names will be revered and honored not only in your generation, but for posterity. The young men of today will be the fathers of the sons who will, with never ending progress in medicine, write the new medical text books of tomorrow.

There have been many changes in medical science since this College was organized 26 years ago by a handful of visionaries. One of the most remarkable accomplishments has been the conquest of tuberculosis. In the United States, the death rate from tuberculosis has declined to a fraction of what it was in 1935, and many sanatoria have closed their doors, or have been converted into hospitals for the non-tuberculous sick.

This has been accomplished with the aid of new medical and surgical weapons which have completely altered the method of treatment of this disease. During your lifetime, tuberculosis can be eliminated or become as rare as smallpox through the application of presently known methods of discovery and treatment of tuberculosis.

There has also been change in treatment of diseases of the heart. Some answers have been found through surgery, for the lesser segments of congenital and rheumatic cardiac disease. There still remains the larger problem of increasing mortality and morbidity, from atherosclerotic cardiovascular disease. Diseases of the coronary arteries are at an all time high, killing more people than any other disorders to which the flesh is heir. Indeed, cardiovascular disease is responsible for more than half of all deaths in this country. Will you contribute to the solution of this problem? Until you do, three of you will die each year and six more will be handicapped by this scourge of the civilized world.

There is still much to be done in solving the acute diseases of the lungs. While pneumonia of pneumococcic etiology has been all but eliminated because of the advent of antibiotics, the pneumonias due to resistant strains of staphylococcus are highly fatal. In addition, virus pneumonia has become more common and adds to the fatality, especially in the elderly. There is still need for therapeutic advance in the treatment of all acute pulmonary diseases.

The chronic, non-tuberculous pulmonary diseases are gradually becoming more and more of a problem. As we live longer, more of us develop significant symptomatic pulmonary emphysema. At present, this is one of our most common pulmonary diseases and one which thus far has defied definite therapy. In a few cases of bullous emphysema, surgery has been of benefit. Perhaps one of you may add to our knowledge and improve our skill in treating the large and growing morbidity from pulmonary emphysema.

The common cold has also continued unchallenged as the most frequent disease encountered at all ages. Each of us has an average of two acute colds a year. While some benefit has been claimed for prophylactic vaccine therapy, using the newer vaccines of Coxsackie and adenovirus type—there has been no general acceptance of this immunization. Indeed people have never taken too readily to any preventive measures of therapy except for their children, and then only bcause the pediatricians have been on the job in insisting that the well babies are brought in regularly for inspection. I hope that all of our members will emulate the pediatricians and remember to continue immunization as the children grow up. In addition to smallpox, pertussis, tetanus and typhoid immunization, prophylactic measures should be taken against the common cold.

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*Presented at the Convocation, 26th Annual Meeting, American College of Chest Physicians, Miami Beach, June 8-12, 1960.

In addition to these problems, the question of cancer of the lungs and bronchi is our special concern.

The rise in crude death rates from primary carcinoma of the lung and bronchi has been vigorously brought to our attention by numerous statistical reports both here and abroad during the last ten years. In spite of an apparent statistical association between cigarette use and bronchogenic carcinoma, the etiological factors of this disease are still obscure. It has thus far not been possible to produce carcinoma of the lung with tobacco smoke. Until the cause of cancer is known, at best only contributory factors can be implicated by association. We must know if this disease is due to one or more viruses, or to disturbed enzyme systems, which under certain stimuli for cellular multiplication, escape normal control mechanisms. Is there something in environment, such as pollution of the air we breathe, which has caused an increase in cancer of the lung? Or is it our diet which has caused the increase in cancer of many organs? Has the background of radioactive fall-out come to avenge the dead at Hiroshima? Are the nations of the world contributing to race suicide by even the peaceful exploitation of atomic energy? All these questions and more will require answers, and you will contribute to the knowledge with which the answers will be found.

If these medical problems are not enough to keep you occupied, your generation must find the answers which will deter our government from taking over the practice of medicine, under the guise of artificial necessity. That the Government of the United States is socialistic needs no elaboration. The only question is how soon will this country embark on the full and complete program of socialized medicine. Unless there is a unified and firm stand by the medical profession, private practice as we know it will not exist in this country in another quarter century. If we pass on to you the freedom of medical practice, will you protect and guard this priceless possession, or will you allow organized minorities and "third-parties" to barter away your rights, to promote their own political power?

And now a final question. This College is an international organization, dedicated to saving human life both here and abroad. To do this, some cure must be found for this madness called "war." Some way must be found to reduce the wanton waste of money, and resources, for purposes of destruction, and to divert these assets into constructive use. This College, as an international organization, can help spread the Gospel of Peace. I know as well as you, that peace is not unilateral. I also know the "cold war" of the last 15 years is not "peace." I believe that in our international association with physicians of other countries, we as members of this College, can promote understanding, and inspire mutual respect. This is the way to "peace."

And now, as I close my remarks, I do not give you the "Keys to the Kingdom." I give you a challenge to work without ceasing—that those who follow you may be blessed by your having gone before. There is an ancient Hebrew saying that "The student, learning from a teacher, is like one candle being lit from another. The second is kindled, yet the flame of the first is not diminished."

Gilbert Keith Chesterton, the English poet, has expressed my philosophy in a poem entitled "Building."

"I watched them tearing a building down,—
A gang of men in a busy town—
With a yo-heave-ho and a lusty yell,
They swung a beam and the side wall fell.
I asked the foreman, "Are these men skilled—
The kind you would hire if you wanted to build?"
He laughed and said, "Why no indeed,
Just common labor is all I need;
They can easily wreck in a day or two
What builders have taken years to do."
I asked myself as I went my way,
"Which of these roles have I tried today?
Am I a builder who works with cars,
Measuring life by the rule and square,
Shaping my deeds by a well made plan,
Patiently doing the best I can?
Or am I a wrecker who walks to town,
Content with the labor of tearing down:"

The College looks hopefully to its young members to carry on the work of the builder. You have our best wishes and fondest hopes for success.

COMMITTEE ON NOMINATIONS

The 27th Annual Meeting of the College will be held in New York City, June 22-26, 1961. The members of the Committee on Nominations for offices to be elected in 1961 are:

Donald R. McKay, Buffalo, New York, Chairman
Elected by the Board of Regents
Alexander Libow, Miami Beach, Florida
Elected by the Board of Governors
Henry C. Sweany, Mt. Vernon, Missouri
Appointed by the President

Recommendations for elective offices may be addressed to: Dr. Donald R. McKay, 1275 Delaware Avenue, Buffalo, New York. The Committee on Nominations will meet in Washington, D. C. on November 28, 1960, during the Interim Session of the College.

COMMITEE ON SCIENTIFIC PROGRAM FOR 1961 ANNUAL MEETING REQUESTS ABSTRACTS OF PAPERS

New York City will be host to the 27th Annual Meeting of the College, June 22-26, 1961. Plans for the scientific program are now under way and physicians interested in presenting papers are invited to submit a 200-word abstract to the Committee on Scientific Program for consideration. These should be addressed to the Executive Offices of the College, 112 East Chestnut Street, Chicago 11, Illinois. Abstracts submitted on or before November 15, 1960 will be reviewed by the Committee when it meets in Washington, D. C. on November 26, 1960.

John F. Briggs, St. Paul, Minnesota
Chairman, Section on Cardiovascular Diseases
H. S. Van Ordstrand, Cleveland, Ohio
Chairman, Section on Pulmonary Diseases

COMMITTEE ON MOTION PICTURES

The Committee on Motion Pictures of the College is interested in learning of new films on diseases of the chest (heart and lungs) for possible presentation at the 27th Annual Meeting of the College in New York City. All pertinent information concerning films may be forwarded to Dr. Paul H. Holinger, chairman of the committee, 112 East Chestnut Street, Chicago 11, Illinois. Those accepted for presentation in the annual motion picture program will be eligible for the 1960 Film Contest and will be referred to the judging committee for review. The Committee on Motion Pictures will also be pleased to review films for official approval and inclusion in the Approved Film List of the American College of Chest Physicians.

CHAPTER NEWS

KENTUCKY CHAPTER

The annual meeting of the Kentucky Chapter will be held on September 20 at the First Christ Church in Louisville. Following is the program:

2:00 p. m. "Cultures of Sputa in Bronchial Asthma"
Lloyd Mayer, Lexington

"Allergic Manifestations in Nontuberculous Chest Diseases"
Armand Cohen, Louisville

"Physiologic Considerations of Pulmonary Emphysema"
Armond T. Gordon, Louisville

Intermission

"Presentation of Five Cases of the Alveolo-Capillary Block Syndrome"
William H. Anderson, Harlan

"Surgery of Pulmonary Emphysema"
Herbert T. Ransdell, Louisville

A dinner meeting will follow, at which Dr. Michael L. Furcolow, Kansas City, Kansas, will speak on "The Emerging Picture of the Epidemiology of Histoplasmosis."

CALENDAR OF EVENTS

National and International Meetings

Sixth International Congress on Diseases of the Chest
Council on International Affairs
American College of Chest Physicians
Vienna, Austria, August 27 — September 1, 1960

Interim Session
American College of Chest Physicians
Washington, D. C., November 26 - 28, 1960

Chapter Meetings

Kentucky Chapter, September 20, 1960

Southern Chapter, St. Louis, Missouri, October 30 - 31, 1960

Postgraduate Courses

15th Annual Course, Clinical Cardiopulmonary Physiology
Chicago, Illinois, October 24 - 28, 1960

13th Annual Course, Recent Advances in Diagnosis and Treatment of Diseases of the Heart and Lungs
New York City, November 14 - 18, 1960